Heme/Onc Resident Manual

2022 – 2023

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2021-2022

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2020-2021

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A Special Thanks

Welcome to the MGH Hematology/Oncology Resident Manual!

This handbook was inspired by requests from housestaff for materials that would help prepare them for oncology floor rotations. Our goal is for this manual to serve as a reference guide for MGH housestaff and other healthcare providers who care for oncology patients. We are indebted to Dr. Jaime Schneider (2018), Dr. Lova Sun (2018), Dr. Evan Chen (2019), and Dr. Katie Mauer (2019) for the creation of the first two editions of this manual.

This edition's authors are listed below each chapter. We would like to thank all of the residents, fellows and pharmacists who served as chapter authors and whose work made this guide possible.

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We would also like to acknowledge our outstanding faculty reviewers for their comments and feedback. We are very fortunate to be working alongside faculty who continually demonstrate an unwavering commitment to teaching and mentorship.

David Kuter
Tem Bendapudi
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Finally, we would like to thank Jay Vyas, Jay Rajagopal, the DOM Chief Residents, and the DOM administrative staff for supporting this endeavor.

Hematology/Oncology is an ever-evolving field and we hope future residents feel empowered to edit this manual. Of course, this guide should be used in conjunction with other resources and not in place of sound clinical judgment. We hope above all that this manual serves to help you provide the highest level of care for our oncology patients.

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Overview of Inpatient Oncology Rotations

- Medicine housestaff rotate through a variety of oncology-based inpatient wards during residency:
  - Interns rotate through solid tumor, lymphoma/myeloma, and (in the first half of the year) leukemia services
  - Juniors (JARs) Lunder night-float (coverage of Lunder 9 patients) and in the second half of the year, on leukemia
  - Seniors (SARs) rotate through solid and lymphoma/myeloma, and (in the first half of the year) leukemia
- Medicine residents will also see oncology patients on the Bigelow general medicine service.
- Lunder rotations follow a traditional team structure in which the intern carries their own list of patients.

Lunder Details and Logistics

- For detailed explanations of housestaff team structures, rotation expectations, and workflow, see the most recent Lunder rotation guide in the **MGH Whitebook App**.
- There are three housestaff admitting services on L9 and L10: solid (L9), lymphoma/myeloma (L9) and leukemia (L10). There is also a BMT team staffed by NPs on L10. Lunder 9 is covered by a JAR overnight, whereas Lunder 10 is covered by a hospitalist / moonlighter.
- Lunder 9 has 32 private patient rooms. The floor is structured like a figure-eight with a low side called the "Green Side" with 16 rooms, evenly numbered from 910 to 944, and a high side called the "Yellow Side" with 16 more, evenly numbered from 960 to 994. Lunder 10 has a similar set up.
- Solid team sits by room 942; Lymphoma/Myeloma team sits in the L9 bubble (a glass windowed room behind the front desk)
- The resource nurses (RRN), nursing director, case managers (CMs), and inpatient administrative coordinator (IAC) sit in the "bubble". The attending nurses (ARNs) are on their respective sides.
- The call rooms for the night junior are in a private hallway across from room 930 (and 1030 on L10) There is a staff restroom just outside the call room. There are four family rooms (with beautiful views of Beacon Hill) available for family meetings and reflections in the four corners of the unit. Rounds are often held in these rooms as well (e.g. Solid rounds on L9, Leukemia rounds on L10).
- The RRN on each floor holds the Lunder 9/10 admitting pager and will let teams know when a patient has been assigned.

Sample Schedule for Lunder onc

- 7AM: pre-round on patient list
- 8AM: round w/ Leukemia attending on any L9 Leukemia patients
- 8:30AM: overflow rounds (L/M patients on solid team, or vis-a-versa)
- 9:00-10:45: rounds with oncology attending
- 11am: T/Th multidisiplimary rounds L9 (SARs)
- 12:15PM: noon conference (if no acute patient issues)

Oncology Patients on the Bigelow

Patients newly diagnosed with cancer often end up on the Bigelow (this may happen less often with COVID related admission guidelines). Patients may present with abnormal blood counts and/or imaging findings, unexplained fevers and/or weight loss, or new localized symptoms (dyspnea, chest pain, headaches, jaundice, abdominal pain, thrombosis) secondary to a suspected mass or new malignancy. Often, the primary team will localize and retrieve tissue when cancer is suspected, but oncology can be consulted for assistance with selecting the most appropriate biopsy site. In general, if there is metastatic disease, biopsy the metastasis rather than the primary as this establishes the diagnosis. However, this is not true for all cases and so if there is any question, consult oncology (e.g. bony metastases are not good biopsy targets when molecular studies are needed for cancer therapy selection, as the decalcification process precludes many molecular studies). Reviewing suspicious radiographic imaging with radiologists may be helpful, as they may be able to expand or narrow the initial differential and recommend the most effective and safe approaches to retrieving tissue. It is important to seek the least invasive measures when possible: FNA and IR-guided biopsies are preferred over bronchoscopy, endoscopy/colonoscopy, or exploratory laparoscopy/laparotomy.

Oncology Consult: On non-oncology services like Bigelow, usually once tissue is retrieved, oncology should be consulted, even if final pathology has not yet resulted, as the oncology teams may be able to expedite pathology review. Sometimes there is no obvious optimal approach for retrieving tissue, and the oncology team may be helpful in partnering with interventionists earlier in the process to expedite biopsy. All new consults are placed through the Partners Paging Directory under "Hematology/Oncology." The fellow on call takes new consults. Residents may check www.amion.com login: MGHCC (case sensitive) for further details on which attendings are on call for specific cancer services. Often an oncology fellow will take the initial consult and staff the patient with the appropriate attending, and then an NP or attending may be the representative from the oncology team that follows the patient. Patients who are admitted to the Bigelow and already have an established outpatient oncologist at MGH will automatically have the "Established Patient" oncology team consulted during their admission.

Important Pearls

- On admission, it is helpful to touch base with the patient's primary outpatient oncologist. Most of the time, they will want to be involved in the patient's care. If the patient has multiple providers (oncologist, radiation oncologist, neuro oncologist, surgical oncologist), it may be helpful to send a multi-disciplinary email to the whole team and provide major updates as the patient's care evolves. Include the APCs (e.g. NP who sees the patient in clinic with the outpatient oncologist) on these emails so they are in the loop about the overall plan for the patient.
- Think about the chemotherapy that your patient is receiving. What are the mechanisms of action? Be familiar with the common side effects.
- Febrile neutropenia is a medical emergency as studies have shown that early antibiotic initiation changes outcomes: treat early and treat appropriately (per MGH Febrile Neutropenia guidelines).
- Acute leukemia is a medical emergency. Think about the patient's presenting symptoms, how the diagnosis was made, and implications on treatment (chemo vs. chemo + transplant?) and prognosis.
- Review imaging with radiologists and your attending in the Dodd Room on the second floor
- Review pathology on multi-headed scope with your attending in the Warren basement
- Think about the underlying molecular diagnostics in the context or your patient's disease: know your patient's karyotype/mutational profile. Does the patient have genetic mutations such as FLT3, NPM1, IDH? Is his/her mutation associated with positive or poor prognostic outcomes?
- Always think about the degree of your patient's immunosuppression. Is he/she neutropenic and if so, how severe? What immunosuppressive medications is he/she on?
- Always keep in mind the overall trajectory of your patient's illness: Is it curable? What are the palliative treatment options? At what point is involving Palliative Care appropriate?
- For transplant patients, think about whether the patient is receiving myeloablative conditioning or reduced intensity conditioning. What is conditioning and what are the goals?
- You will start to see more patients receiving immunotherapy and CAR-T cells at MGH. Complications can sometimes be fatal and treating them is challenging. Always have a low threshold to involve the primary oncologist for decisions about how to treat complications related to immune dysregulation. Patients who have developed autoimmune complications from their checkpoint inhibitor therapies will receive consultation from the Severe Immunotherapy Complications (SIC) service, a multi-disciplinary service that aims to recognize atypical presentations of toxicity and set best practices in management.
- To see chemotherapy regimen and trials, wrench in the "Springboard" function in Epic.

Interdisciplinary Care Team

Care on the oncology wards is team-based, patient-centered, and multidisciplinary. Oncology patients are medically and psychosocially complex and thus require a comprehensive collaborative approach to provide the best care possible. Residents will work closely with a variety of services including (but not limited to): nursing, social work, palliative care, infectious disease, radiation oncology, radiology, spiritual care/chaplaincy, pharmacy, physical therapy, occupational therapy, nutrition, speech/swallow therapy, surgery, pulmonary, gastroenterology, etc. Rounds are meant to bring many of these voices to the table to help achieve our goal of providing multi-disciplinary and comprehensive care.

Lunder Rounding Structure

Before rounds, residents are expected to have seen all the patients on their list and have a tentative plan in mind. Therefore, residents typically pre-rounds from 7:00 to 9:00 am. Consults should also be called before 9:00 am if possible and anyone scheduled for studies or interventions should have their calendars confirmed. Any patients going home should have their discharges prepared before 9:00 am as well. If a team has patients on their list with a malignancy that is not their native team's disease site (e.g. lymphoma/myeloma team has a solid tumor patient) then that team will need to coordinate a time to round with that disease site attending (e.g. after lymphoma/myeloma team rounds have conclude, the intern +/- SAR can go to solid rounds if still ongoing or simply touch base with the solid attending whenever the chance arises).

Rounds are structured in SOAP format for each patient. The overnight events, subjective, and objective are provided by the intern (or medical student). The objective data can be run by the intern or the JAR/SAR. The intern will present his/her problem-based assessment and plan. As plans are discussed, the nurses bring up any concerns that the patient has expressed or any issues that had come up overnight. The pharmacist will also discuss chemotherapy start times and consents.

During rounds, in addition to the attending and medical team, the following individuals are present:

- Attending nurse: There is an attending nurse on each side of the unit (high side and low side). They work from 7 am to 3 pm but are often around earlier and later than their specified shifts. It is their job to know something about all the patients on

their side. They are meant to provide continuity for the patients and keep in mind the big picture issues such as disposition, prognosis, family dynamics, and goals of care. They also act as a liaison between the medical team and the CMs. Each patient may have a different nurse on different days and a new resident team every two weeks; however, the attending nurse does not change. This is very helpful for patients who spend many weeks on Lunder. **If there is a change in care plan for a patient, ensure that the ARN is up to date as soon as possible.**

- IAC: The IAC coordinates discharge medications and follow-up appointments and performs prior authorizations, which are often required for narcotics, anti-psychotics (olanzapine), growth factor medications, and certain chemotherapies. **Send down medications to the MGH Outpatient Pharmacy as soon as possible to ensure prior authorization does not hold up discharge.**
- Pharmacist: The pharmacists on Lunder have done their residencies in oncologic pharmacology. They are excellent resources for dosing antibiotics and chemotherapy, reminding us about important prophylactic medications the patients should be on, and sharing information on drug-drug interactions that we may not be familiar with in general medicine. **Use them as a resource when dosing medications with which you are unfamiliar.**
- Nurses: The patient's nurse is present on rounds and brings his or her own set of concerns about the patient and may ask the responding clinician to change orders or optimize certain processes after the plan has been run. They also act as the voice of the patients, who are not present during rounds. **Closed loop communication with nurses and pre-emptive Voalting can reduce the number of pages and frustrations during the day.**

Importantly, the patients' primary oncologists cannot round on the patient daily and are not present during the team rounds in the mornings. However, they are intimately involved in the patients' care. They usually have the best idea of the patient's long-term chemotherapy plans and prognosis and may have certain goals for the admission. **The inpatient team is responsible for communicating with the outpatient primary oncologist and keeping them in the loop (along with the APCs).**

Other members of the team, who are not on rounds but present on the floor or in clinic:

- Nursing Director: The nursing director oversees the operations of the entire floor, including budget, hiring, policies, etc. She is not as involved in day-to-day patient care; however, she is the administrator of the unit at large.
- Clinical Nursing Specialist: The clinical nursing specialist oversees education for the nurses on the floor and fills them in on how to adjust in the setting of new therapies coming down the line, medication shortages, fluid shortages, etc. He/she is also the wound specialist.
- Oncology Advanced Practice Clinicians (APCs): The MGHCC's large specialized advanced practice team includes Inpatient Oncology Nurse Practitioners who provide responding clinician coverage and consult, as well as Ambulatory Oncology APCs who practice in disease specific specialty areas and partner with the patient's oncologist for ongoing care. The APCs facilitate admissions into the hospital and advise on specifics around discharge.

Tips for Interdisciplinary Care Team Dynamics (discussed with Lunder 9 ARN Sarah Brown)

- Communication – it is important to remember we are all one team taking care of the patient
  - Be open about chemotherapy plans, prognosis, end-of-life, and oncologic emergencies
  - Explain any new orders to the RNs so they do not have to page to ask about them
  - Check in with RNs in the PM before leaving on short call or if there are no admissions
  - Coordinate timing of family meetings, radiation therapy, procedures, and discharges so that nurses with multiple patients can plan their days
  - Make sure nurses are aware when you start family meetings even if they cannot join
  - If something new comes up in a family meeting or discussion with a consultant and the RN is not present, document it in a timely manner or loop everyone in.
- Acknowledge the expertise and experience of RNs that have been working with oncology patients for years: they know things about chemotherapy and end-of-life discussions that may be helpful to us; do not be afraid of asking questions.
- When it comes to symptom management, the oncology patient population is different from other patients in the hospital – take the RNs seriously when they're concerned about pain, air hunger, and nausea. They have years of experience and if they have a bad feeling about something, take it seriously and follow up.

Approach to Discharge

There are several possible dispositions for patients after their time in the hospital and there are special considerations that should be kept in mind for each:

- Home: If a patient is going home, then it is important to have an accurate, up-to-date pharmacy on file and to ask patients what medicines they need refilled in addition to any new medicines started in the hospital. Some new medicines may be

unaffordable for the patient without a prior authorization (PA); the IAC can help identify these medicines and complete the PA. A follow up appointment with the outpatient oncologist should be made prior to discharge; the IAC will help with this also.

- Home with services: It is imperative to know whether patients will need any services at home: VNA, PT, transfusion services (for IV antibiotics or TPN), medical equipment, oxygen, etc. The therapists will give recommendations and the CMs will set these up. There may be paper scripts to sign. The sooner this can be determined, the more streamlined the discharge process. Transfusion services, line care teaching, Lovenox teaching, and delivery of equipment may take 24-48 hours to set up, so if a patient is planned for discharge on the weekend, these services should be discussed on Thursday at the latest.
- Skilled nursing facility (SNF): Most nursing facilities can provide the medications that are provided to patients in the hospital, except for specific chemotherapies and palliative medications. The CMs can help identify which medicines will need paper scripts printed at the time of discharge. The others will be "no print" in the EPIC discharge module. Any patient going to SNF will need their hospital course/ discharge summary completed prior to discharge.
- Rehab: A patient that has been in the hospital for a certain amount of time and/or been to the ICU during the course of their admission may qualify for long term acute care (LTAC) or inpatient rehabilitation at a facility like Spaulding Cambridge, where the team has capabilities to provide chemotherapy infusions and intensive physical therapy. Generally, no specific orders are needed for these discharges except for clearly written instructions in the hospital course on the start/ stop time for certain chemotherapy agents. Growth factor medications may still need to be ordered separately and provided by the family themselves.
- Hospice at home: Patients and families that would like to go home with hospice must have enough support for 24-hour care at home and must meet with an agency that services their geographic area prior to discharge. The final discharge, including delivery of a hospital bed and other necessary equipment, takes 2-3 days to arrange. Once the medical team and patient/ family are clear on the patient's wishes, the intern should let the CM know, and the CM can then approach the patient and their family with more information about hospice and ask them to choose an agency. Then an agency representative meets with the family and the next day discharge can be arranged.
- Hospice in a facility: Some patients are very sick and qualify for inpatient hospice at a facility. This entails being on IV pain control or air hunger control. Often this requires out-of-pocket payment for room and board unless a patient has Medicaid in addition to Medicare. A patient's family will explore facilities that are close to their home and let the CM know which one meets their needs. A hospice representative may facilitate the discharge in this case as well
- GIP: Some patients are so sick that they may pass away imminently and the best option for them and their families is to stay at MGH for inpatient level hospice care. If a patient meets these criteria, palliative care will tell the team to consult hospice, and a representative from Care Dimensions will meet with the patient and family, confirm that they qualify, and then tell the medical team to discharge the patient. The patient stays in the same room, but the GIP palliative care team becomes primary and readmits the patient to the hospital under "hospice." The Senior On may be called to pronounce these patients overnight.

Tips for Discharges (with contributions from Cedric Cooper, Lunder 9 Case Manager)

- If possible, book 30 minutes with the case managers on the first day of the whole new team's rotation (usually Thursday) for mutual introductions, team-building, and an overview of why discharge planning can be more challenging with this specific patient population
- Be mindful that when the case managers ask us to perform a task or check in with a patient or consultant about something, it is usually an imperative task that must be done in a timely manner and that cannot be overlooked before the end of the day; otherwise, it may delay a patient's discharge. An example is emailing the primary oncologist to know whether chemotherapy is planned for the next month to ascertain whether a certain rehab/ SNF facility will accept the patient or not (some SNFs do not take patients with active chemotherapy plans as they are not trained to manage the adverse effects associated with chemotherapy). Another example is touching base with the Infectious Diseases team about treatment course and filling out infusion paperwork for the company that will be providing IV antibiotics to a patient when he/she leaves.
- Communicate in a way that is "firm but pliable" with patients about their impending discharge. Once we reach "medical readiness", the mantra should be, "and you are ready to leave the hospital in the next 24-28 hours." Otherwise, it can become very difficult to discharge patients, who feel well cared for and safe on Lunder as compared to at home or outside the hospital.

Below are common chemotherapy regimens you may see on Lunder + indications for growth factor. **There is MUCH more info in the disease specific chapters – this is meant as a quick easy reference**. When possible, regimens are hyperlinked to corresponding British Columbia (BC) Cancer Protocol pages for more info on supportive care and baseline tests. Each drug name is hyperlinked to BC Cancer Manual Drug Monographs for more on mechanism, pharmacology and adverse events (AEs). A few interesting AEs have hyperlinks to pertinent papers/pictures. Day indicates the day in the cycle the drug is given (cycles are generally 21d). Emetic potential is generally not included among AEs given relative ubiquity and ppx built into chemo orders.

Lymphoma

R- CHOP

Drug	Day	Key AEs
(R) Rituximab	1	Infusion reactions, HBV & TB reactivation
(C) Cyclophosphamide	1	Hemorrhagic cystitis (IVFs & MESNA ppx), cardiotoxicity, IPF
(H) Doxorubicin	1	Cardiotoxicity (esp ↓ EF)
(O) Vincristine	1	Neuropathy: peripheral > autonomic or central; constipation
(P) Prednisone	1-5	Hyperglycemia, HTN in elderly

DA-EPOCH-R DA = "dose adjusted": dosing of E, C & H based on Plt and PMN nadirs between cycles.

Drug	Day	Key AEs
(E) Etoposide	1-4	Hypotension (during infusion)
(P) Prednisone	1-5	Hyperglycemia, HTN in elderly
(O) Vincristine	1-4	Neuropathy: peripheral > autonomic, central; constipation
(C) Cyclophosphamide	5	Hemorrhagic cystitis (IVFs & MESNA ppx), cardiotoxicity, IPF
(H) Doxorubicin	1-4	Cardiotoxicity (esp ↓ EF), mucositis
(R) Rituximab	1	Infusion reactions, HBV & TB reactivation

Venetoclax

Drug	Day	Key AEs
Venetoclax	Continuous	TLS (slow dose escalation), CYP3A4 & PGP substrate, diarrhea

R-ICE

Drug	Day	Key AEs
(R) Rituximab	1	Infusion reactions, HBV & TB reactivation
(I) Ifosfamide	2	Hemorrhagic cystitis (IVFs & MESNA ppx), encephalopathy, CINV
(C) Carboplatin	2	Allergic reactions, peripheral neuropathy, nephrotoxicity, thrombocytopenia
(E) Etoposide	1-3	Allergic reactions, hypotension (during infusion)

R-DHAP, R-DHAX (R-DHAOX), or R-DHAC P, X or C given depending on regimen

Drug	Day	Key AEs
(R) Rituximab	1	Infusion reactions, HBV & TB reactivation
(HA) Cytarabine, high dose	2	Cytarabine syndrome (fevers + flu-like), chemical conjunctivitis (steroid eye drops for ppx), cerebellar neurotoxicity (daily neuro exam), rash
(P) Cisplatin	1	CINV, K/Mg/Ca wasting, AKI (IVF required), ototoxicity, neuropathy
(X) Oxaliplatin	1	Peripheral neuropathy (cold-induced in first 5 days)
(C) Carboplatin	1	Allergic reactions, peripheral neuropathy, nephrotoxicity, thrombocytopenia

R-CODOX-M

Drug	Day	Key AEs
(R) Rituximab	1	Infusion reactions, HBV & TB reactivation
(C) Cyclophosphamide	1 & 2	Hemorrhagic cystitis (IVFs & MESNA ppx), cardiotoxicity, IPF
(C) Cytarabine (IT)	1, 3†, 5‡	Mild nausea, vomiting, fever
(O) Vincristine	1, 10	Neuropathy: peripheral > autonomic or central; constipation
(DOX) Doxorubicin	1	Cardiotoxicity (esp ↓ EF), mucositis
(M) Methotrexate (IV), high dose	10	Renal failure (IVF + HCO_3 ppx), transaminitis, mucositis, myelosuppression (leucovorin rescue)
Methotrexate (IT)	1, 10‡	Aseptic meningitis, transverse myelopathy

R-IVAC

Drug	Day	Key AEs
(R) Rituximab	1	Infusion reactions, HBV & TB reactivation
(I) Ifosfamide	1-5	Hemorrhagic cystitis (IVFs & MESNA ppx), encephalopathy, CINV
(V) Etoposide	1-5	Hypotension (during infusion)
(AC) Cytarabine, high dose	1-2	Cytarabine syndrome (fevers + flu-like), chemical conjunctivitis (steroid eye drops for ppx), cerebellar neurotoxicity (daily neuro exam), rash
Methotrexate (IT)	5	Aseptic meningitis, transverse myelopathy

R-CODOX-M/R-IVAC

- R-CODOX-M cycles may alternate with R-IVAC (if high-risk disease), with the number of cycles of each, and cycle components dependent on disease risk († indicates only with high risk) and CNS involvement (‡ indicates only with CNS involvement).

Leukemia

7 + 3 (induction for AML)

- 7d cytarabine & 3d of anthracycline (Idarubicin or Daunorubicin)
- Midostaurin 50mg BID days 8-21 if FLT3 positive. Watch QTc, nausea/diarrhea, rash, muscle pain
- Gemtuzumab Ozogamicin 3 mg/m2 on day 1 if CD33+ or core-binding factor leukemia. Watch for QTc, TLS, VOD/SOS

Drug	Day	Key AEs
Idarubicin or Daunorubicin	1-3	Cardiotoxicity (↓ EF, arrythmia), mucositis
Cytarabine	1-7	Fevers, cytarabine syndrome (fever + flu-like), mucositis, rash, palmer plantar erythrodesia

HiDAC (Hi-Dose AraC) (consolidation for AML)

Drug	Day	Key AEs
Cytarabine	1, 3, 5	Fevers, cytarabine syndrome (fevers + flu-like), chemical conjunctivitis (steroid eye drops for ppx), cerebellar neurotoxicity (daily neuro exam), rash, palmer plantar erythrodesia

HyperCVAD (induction/consolidation for ALL)

- 8 cycles total: Schedule A drugs w/ odd cycles (1, 3, 5, 7); Schedule B w/ even cycles (2,4,6,8)
- Rituximab added if CD20 positive, TKI added if BCR-ABL t(9;21) positive. GCSF used.

Schedule A Drug	Day	Key AEs
(C) Cyclophosphamide	1-3	Hemorrhagic cystitis (low risk w/ hyperCVAD dosing), cardiotoxicity, IPF
(V) Vincristine	4, 11	Constipation, neuropathy: peripheral > autonomic, central
(A) Doxorubicin	4	Cardiotoxicity (esp ↓ EF), mucositis
(D) Dexamethasone	1-4, 11-15	Hyperglycemia, HTN in elderly

Schedule B Drug	Day	Key AEs
Methotrexate	1-2	Renal failure (IVF + HCO_3 ppx), Pneumonitis, Neurotoxicity
Cytarabine	2-3	Fevers, cytarabine syndrome, rash, palmar plantar erythrodysesthesia
Methylprednisolone	1-3	Hyperglycemia, HTN in elderly

HMA/Venetoclax (Induction for AML in the elderly)

- HMA (hypomethylating agent) can be Azacitadine or Decitabine

Drug	Day	Key AEs
Venetoclax	Continuous	TLS (slow dose escalation), CYP3A4 & PGP substrate, diarrhea
Azacitadine OR Decitabine	1-7 1-10	AKI, renal tubular dysfunction (low K, Na, PO_4, bicarb), constipation

AYA (Induction for ALL)

- Add desatinib (†) if Ph-chromosome positive; Add Pegasperginase (‡) if Ph-chromosome negative.

Drug	Day	Key AEs
Cytarabine (IT)	1	Mild nausea, vomiting, fever
Doxorubicin	1-2	Cardiotoxicity (esp ↓ EF)
Vincristine	1,8,15,22	Neuropathy: peripheral > autonomic, central; constipation
Methotrexate	3	Renal failure (IVF + HCO_3 ppx), Pneumonitis, Neurotoxicity
Prednisone	1-29	Hyperglycemia
Desatinib†	daily	Diarrhea, fluid retention (edema, pleural effusions), rashes
Pegasperginase‡	4	Thrombosis (monitor AT3), pancreatitis, hypersensitivity

BMT

Mel/Flu Conditioning

Drug	Day	Key AEs
Melphalan	-2	Hypersensitivity reactions, mucositis, pneumonitis/IPF, delayed diarrhea
Fludarabine	-7, -6, -5, -4, -3	Fevers, pulmonary toxicity, delayed neurotoxicity, AIHA

RIC Cy/Flu or Bu/Flu: Reduced Intensity Conditioning Cytoxan/Fludarabine or Busulfan/Fludarabine

- Used in combination w/ total body irradiation (TBI) or Anti-thymocyte globulin (ATG)
- For Bu/Flu, Busulfan given Day -6, -5. AEs: mucositis, fevers, rash, diarrhea

Drug	Day	Key AEs
Cyclophosphamide	-6, -5	Hemorrhagic cystitis (IVFs & MESNA ppx), IPF, cardiotoxicity (↓ EKG voltage, cardiogenic shock, tamponade).
Fludarabine	-6, -5, -4, -3, -2	Fevers, pulmonary toxicity, delayed neurotoxicity, AIHA

BEAM Conditioning

Drug	Day	Key AEs
(B) Carmustine	-6	Pneumonitis (early), pulmonary fibrosis (late)
(E) Etoposide	-5, -4, -3, -2	Hypersensitivity reactions, hypotension (during infusion)
(A) Cytarabine	-5, -4, -3, -2	Cytarabine syndrome (fever, flu-like symptoms), rash, lower risk of ocular and neuro toxicity compared to high-dose
(M) Melphalan	-1	hypersensitivity reactions, mucositis, pneumonitis/IPF, delayed diarrhea

TBC Conditioning (for auto transplant)

Drug	Day	Key AEs
(T) Thiotepa	-9, -8, -7	mucositis
(B) Busulfan	-6, -5, -4	mucositis, fevers, rash, diarrhea
(C) Cyclophosphamide	-3, -2	hemorrhagic cystitis (IVFs & MESNA ppx), IPF, cardiotoxicity (↓ EKG voltage, cardiogenic shock, tamponade).

Melphalan Conditioning (for auto transplant)

Drug	Day	Key AEs
Melphalan	-1	Hypersensitivity reactions, mucositis, pneumonitis/IPF, delayed diarrhea

Solid Tumor Regimens

FOLFOX

Drug	Day	Key AEs
(FOL) Folinic Acid	1	Also called "leucovorin"
(F) 5-Fluorouracil, 5FU	1-2	Cardiotoxicity, coronary vasospasm, mucositis, diarrhea, plantar-palmar erythrodysesthesia (DPD deficiency can exacerbate)
(OX) Oxaliplatin	1	peripheral neuropathy (cold-induced in first 5 days)

High dose Ifosfamide

Drug	Day	Key AEs
Ifosfamide	1-5	hemorrhagic cystitis (IVFs & MESNA ppx), encephalopathy, CINV

High dose Methotrexate MTX level < 1uM prior to discharge (exact level, attending dependent)

Drug	Day	Key AEs
Methotrexate	1	Renal failure (IVF + HCO_3 ppx), transaminitis, mucositis, myelosuppression (requires leucovorin rescue)
Leucovorin	2 -	"rescue"; given until MTX level undetectable (<0.1 mcM)

And finally, when do patients need growth factor (Neulasta, Granix, etc)?

Growth factor is given for primary prophylaxis if:

(1) Regimen with > 20% incidence of neutropenic fever (includes DHAP, CODOX-M/IVAC, Mini-BEAM; most recent NCCN list here (page MGF-A to B) and ASCO list here)

(2) Regimen with 10-20% incidence of neutropenic fever (including CHOP+/-R, carboplatin/paclitaxel, EC) and 1 risk factors (>65 years, poor performance status, prior episodes of FN, concomitant XRT, BM involvement, extensive prior treatments, wounds/infection, poor nutrition status, advanced disease, serious co-morbidities)

(3) Dose-dense regimens (includes AC-T, RCHOP14)

Anemia Overview

- Clinical manifestations**: ↓O2 delivery**: fatigue, DOE, claudication, cramps, lightheadedness, angina (if CAD), GI sx, pallor (skin, MM); **compensatory mechanisms**: ↑CO (↑HR, ↑pulsations, flow murmurs, tinnitus; eventually → high-output HF), ↑RR, ↑erythropoiesis (sternal tenderness, bone pains) (**Williams Hematology. 9th ed, 2015**).
- Initial workup: CBC w/ diff (MCV, RDW, Δs in other cell lines), smear, retic. count → **calculate** reticulocyte index (RI)**:** adjusts for Hct & early release of retics = *[retic. ct x (Hct/nml Hct)]/maturation factor]*

Overview: Approach to anemia

ANEMIA		
UNDERPRODUCTION: RI < 2%		
MICROCYTIC: MCV<80	**NORMOCYTIC: MCV 80-100**	**MACROCYTIC: MCV>100**
Workup: Fe, TIBC, ferritin **Iron deficiency anemia (IDA):** • ↓Fe, ↑TIBC, Fe/TIBC<18%, ↓ferritin (<30 most sp.; <15 = absent BM Fe); MCV/RBC>13, ↑RDW **Anemia of chronic inflamm.:** • ↓Fe, ↓TIBC, Fe/TIBC>18%, ↑ferritin (if <100 or if <300 in CHF/CKD = Fe defic.); can be normocytic, MCV<70 rare • Usually 1-2mo. to develop but ↓Hb 2-3g/dL in 1-2d in acute illness **Thalassemias:** • MCV/RBC<13 (Mentzner index; 60% se. & 98% sp[2]). MCV often <70 • Abnormal Hb electrophoresis • Mediterranean/Asian/African **Sideroblastic:** • ↑Fe, nml TIBC, Fe/TIBC>30%, ↑ ferritin; smear: basophilic stippling; BM Bx: ringed sideroblasts	**Workup:** Fe, TIBC, ferritin, Cr, TSH, B12, folate, ESR/CRP; ± SPEP/SFLC, AM testost., Epo, BM Bx **Early IDA & anemia of inflamm.** **Mixed:** Fe + folate/B12-defic = "dimorphic" → normocytic, ↑RDW **Chronic kidney disease:** ↓Epo • Tx: Epo ± IV Fe (if Fe/TIBC<30%, ferritin <300) to goal *Hb 10-11* **Endocrinopathies:** • ↓met. rate→↓O2 demand →↓Epo • Thyroid, pituitary, parathyroid, adrenal; hypogonadism (↓ testost.) **Bone marrow:** RBC aplasia, AA, MM, PNH, MDS, myelophthisis Pure RBC aplasia: • Destruction of RBC progenitors (inherited [DBA], autoimmune, thymoma, CLL, parvoB19, MDS, meds) • Dx: reticulocytopenia (<10,000) & BM Bx w/ few/absent RBC precursors, other cell lines nml	**Workup**: folate, B12, LFTs, TSH; ± SPEP/SFLC, BM Bx if unrevealing **Nonmegaloblastic:** <5% hyperseg. PMNs on smear; MCV rarely >110; LDH & bilirubin usually nml • Reticulocytosis • Liver disease, EtOH • Hypothyroidism • AA, MDS, MM **Megaloblastic:** >5% hyperseg. PMNs on smear, MCV usually >110; ↑ LDH & bilirubin • Folate or B12 deficiency • Meds: *antifolates* (MTX, pyrimethamine, TMP, sulfasalazine), *purine/pyrimidine analogs* (6-MP, 6-TG, AZT, acyclovir; 5-FU, AZT), *AEDs* (phenytoin, phenobarb., primidone, carbamazepine), hydroxyurea, cytarabine, OCPs, PPIs, metformin, colchicine, arsenic
INCREASED DESTRUCTION: RI > 2%		
Workup: LDH, bilirubin, haptoglobin, DAT, smear Intravascular hemolysis: ↑↑LDH, ↓↓haptoglobin, hemoglobinuria, hemosiderinuria, hemoglobinemia Extravascular hemolysis: ↑ ind. bili ± ↑ LDH, ± ↓ haptoglobin (if free Hb escapes spleen), splenomegaly		

EXTRINSIC				INTRINSIC			
Immune-mediated	**Mechanical**	**Hyper-splenism**	**Infectious/ chemical**	**PNH**	**Enzyme defect**	**Membrane defect**	**Hemoglobin-opathies**
• Warm AIHA • Cold AIHA • Drugs	• Microvasc. • Macrovasc.	• Congestion • Infection • Inflamm. • Infiltration	• Direct infection • Toxins	• HSC defect	• G6PD defic. • PK defic.	• Hered. sphero/elliptocytosis • Spur cell	• Sickle cell • HbC • HbD • Thalassemias
ACQUIRED				HEREDITARY			

Iron Deficiency Anemia (NEJM 2014; 371:1324-31)

- Clinical manifestations: angular cheilosis, koilonychia, glossitis, pica, Plummer-Vinson syndrome (IDA, esophageal web, atrophic glossitis), restless legs syndrome
- Etiologies: ↑ **demand** (pregnancy, Epo), ↑**loss** (*GI* [GIB, PUD, CA], GU [menses, hematuria, chronic intravasc. Hemolysis → hemoglobinuria], resp. tract); ↓**intake/absorption** (diet, malabsorption [celiac, IBD, gastric bypass, H. pylori, achlorhydria/chronic PPI]); rarely, genetic iron-refractory IDA (IRIDA) (NEJM 2015;372:1832)
- Workup: GI bleed eval., H. Pylori, consider celiac labs (esp. if refractory to PO iron)
- Tx: PO > IV unless intolerant to PO, malabsorption, Epo in CKD, excess. losses; **PO FeSO4:** 325mg x 1-3 daily or QOD[4]; 6wks to correct anemia, 6mo. to replete stores; best absorbed in acidic environment (i.e. with ascorbic acid, on empty stomach, avoid Ca and antacids); *side effects*: abd. pain, constipation, n/v; **IV iron:** calc. *Fe deficit* (body wt [kg]*2.3*[goal Hb – actual Hb] + 500) & replete (max = 1000mg); *Venofer (Fe-sucrose) 200mg QOD x5 or 300mg QOD x3 or Feraheme 510mcg qweek x2*

Anemia of Chronic Inflammation

- Pathophysiology: ↑IL-6 → ↑hepcidin → ↓*Fe abs. & release*; ↑IL-1 → ↓*Epo*
- Etiology: infection, malignancy, inflammation (autoimmune dz, CHF, CKD)
- Tx: treat underlying cause; Fe if also Fe-deficiency (ferritin <100 [or <300 in CHF/CKD], Fe/TIBC<20%) (Lancet Haematol 2017;4:524); Epo if anemia assoc. with HIV therapy (Ann Intern Med 1992; 117:739) esp. if Epo <500; use of Epo in cancer

controversial (↓RBC transfusions but may ↑VTE risk) (**Cochrane 2012; 12:CD003407**): *ASH/ASCO guidelines recommend only in patients with chemo-associated anemia with Hb <10* (**Blood 2010; 116:4045**); evidence *against* use of Epo in HF (**NEJM 2013;368:1210**).

Thalassemias

- Severe dz: extramedullary hematopoiesis (chipmunk facies, fractures, HSM), Fe overload (endocrine abnlities), high-output HF, hemolysis (gallstones)
- Tx: folate; transfusions + Fe chelator; endocrine support (thyroid, growth, sex hormones; osteoclast inhibitors); allo-HSCT is curative

Features of the Thalassemias (**Ann Hem 2007; 86:487**):

Type	Defect	MCV	Hb	Electrophoresis	Other Features
β thalassemia: defect in 1-2β genes on Chr 11; excess α precipitates in precursors → dyserythropoiesis					
Major	β^o/β^o	50-75	<7	↑ A_2	Severe; transfusion-dep.
Intermedia	β^+/β^+ (or other)	50-75	<9	↑ A_2	Target cells
Minor	β/β^o	65-75	9-10	↑ A_2	Target cells
α thalassemia: defect in 1-4α genes on Chr 16; excess β precipitates in older RBCs → hemolysis					
Silent	3α: αα/α-	80-85	12-14	Normal	
Trait	2α: αα/-- or α-/α-	65-75	12-13	Normal	
HbH	1α: α-/--	60-69	8-9	HbH	Hemolysis, splenomegaly
Hb Bart's	0α: --/--			HbH, Bart's	Hydrops fetalis

β^o = absence of β; β^+ = partial deficiency; - = absence of α

Sideroblastic Anemias

- Pathophysiology: defective heme synthesis → ineffective erythropoiesis, RBC precursors accumulate mitochondrial Fe → anemia, ringed sideroblasts in BM
- Etiologies: **acquired**: EtOH, lead, Cu defic. (can be induced by Zn), drugs (INH, pyrazinamide, chloramphenicol), primary (MDS); mechanism of many drugs is *pyridoxine (B6) antagonism/deficiency*; **heritable**: most common = X-linked deficiency in ALAS
- Tx: remove offending agent; *pyridoxine (up to 200mg/d)*; transfusions + Fe chelator

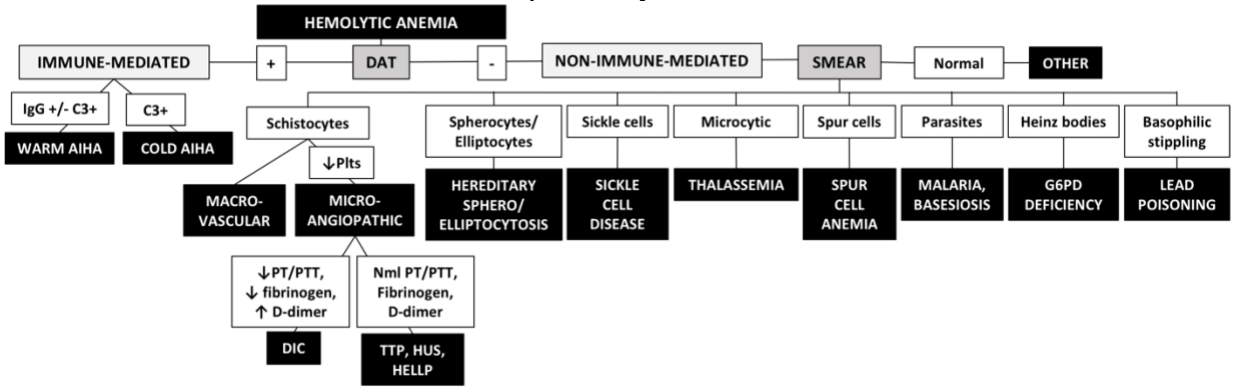
Folate Deficiency

- Clinical manifestations: glossitis, mouth ulcers; ↑homocysteine, *nml* MMA
- Etiologies: ↓**intake**: elderly, poor, alcoholic (wine & whiskey > beer [has folate]); ↓**absorption (jejunum):** celiac/tropical sprue, Crohn's, enteritis, resection, leukemic/lymph. infiltration, Whipple's, scleroderma, amyloidosis, DM; ↑**demand**: pregnancy, ↑BM turnover (e.g. hemolytic anemia)
- Tx: *1-5mg folic acid/day* (check for ↓B12 first: folate corrects heme abnlity; not neuro)

B12 Deficiency (**NEJM 2013; 368:149**)

- Dx: <200 pg/ml = deficiency; 200-350 pg/ml = borderline, ✓ MMA and homocysteine (both ↑)
- Clinical manifestations: glossitis, *subacute combined degeneration* (progressive weakness, sensory ataxia, paresthesias), neuropsychiatric manifestations (↓mood, dementia, "megaloblastic madness")
- Etiologies: ↓**intake**: malnutrition, no dairy/eggs; ↓**absorption:** stomach: *pernicious anemia*, gastrectomy/RYGB, atrophic gastritis, PPIs (**JAMA 2013; 310:2435**); pancreas: chronic pancreatitis; ileum: resection, Crohn's, sprue; ↑**competition:** stasis (blind loop), ↓motility (scleroderma, amyloid); tapeworm
  - ***Pernicious anemia***: Ab to IF → ↓*B12 abs.*; Ab to parietal cell H/K ATPase → achlorhydria, *atrophic gastritis*; **Dx**: anti-IF antibody (specific), ↑fasting gastrin
- Tx: *1000mcg/d IM x 1-2wk → q wk x4-6wk → q mo.;* if neuro sx: *1000mcg q 2wks x 6mo.;* PO B12 = IM/SQ if not due to malabsorption

Workup of hemolytic anemias:



Immune-Mediated Hemolytic Anemia

- Pathophysiology: Ab to RBCs → IgG *opsonization* (partial phagocytosis in spleen → **spherocytes**) or *complement* (IgM>>IgG); **IgG antibodies** = "warm agglutinins" (react at room temperature), *80-90% of AIHA;* **IgM antibodies** = "cold agglutinins" (react below core body temperature)
- Dx: *DAT+* (washed RBCs + Ab against IgG & C3 → agglutination), *spherocytosis*; **warm**: DAT+ for IgG ± C3; **cold**: DAT+ for C3, high cold agglutinin titer (>1:512); **false neg.:** low IgG ("DAT-neg. AIHA"); **false pos.:** transiently +DAT after RBC transfusion

Warm Autoimmune Hemolytic Anemia

- Etiologies: idiopathic (most common), lymphoma, CLL, SLE, CVID, hyper-IgM, HIV; *Evan's syndrome* = two immune cytopenias (usually AIHA + immune thrombocytopenia)
- Tx: glucocorticoids (***prednisone 1-1.5mg/kg/d***; when stabilizes, taper 5mg/wk to *15mg/d*; if severe/rapid, *IV methylprednisolone 100-200mg/d x2w* (**Haematologica 2014; 99:1547**); if fails (20-30%), rituximab vs. splenectomy; 3rd line therapies: cytotoxic agents (Cyclophosphamide, AZA), IVIG

Cold Autoimmune Hemolytic Anemia

- Pathophysiology: if thermal amplitude reached, Ab binds → complement → phagocytosis of C3b-coated cells in spleen/liver or direct lysis (MAC); occurs in superficial vessels of extremities (↓ temp.)
  - **Chronic syndrome** usually due to extravascular hemolysis in spleen/liver
  - **Acute episodes** of intravascular hemolysis occur due to chilling or complement activation (acute phase responses: trauma, fever, surgery) → direct lysis
- Clinical manifestations: acrocyanosis (finger tips, toes, nose, ears), livedo reticularis
- Etiologies: idiopathic, post-infectious (Mycoplasma, EBV), WM, malignancy (CLL, lymphoma)
  - **Paroxysmal cold hemoglobinuria**: cold-reactive *IgG* (Donath-Landsteiner) due to viral infection, syphilis; hemolysis following cold exposure; *no agglutination, so cold agglutinins negative*
- Workup: cold agglutinins titer; if ↑, eval for infection (EBV, Mycoplasma), autoimmune dz (SLE, RA), lymphoma (serum Ig classes, SPEP/SFLC, BM aspirate/Bx with flow cytometry)
- Tx: *avoid cold*; rituximab if symptomatic

Drug-Induced Hemolytic Anemia

- Hapten-induced: *DAT IgG+*; Ab to drug firmly bound to RBC; ex: PCN, cephalosporins
- Immune complex: *DAT C3+*; Ab binds to RBC and loosely bound drug; ex: quinine, rifampin, cimetidine, diclofenac
- AutoAb: *DAT IgG+*; drug induces autoAb to RBC; ex: methyldopa, L-dopa, fludarabine
- Nonimmunologic protein adsorption: *DAT neg.;* drug-induced non-specific binding of plasma proteins (including Ig, complement) to RBC; no hemolysis; ex: cephalosporins, oxaliplatin

Mechanical Hemolytic Anemias

- Pathophysiology**:** RBCs forced at high shear stress through partial vascular occlusions or abnl vascular surfaces; can occur in microcirculation (microangiopathic) or macrocirculation
- Dx**:** findings of intravascular hemolysis (↑LDH, ↓haptoglobin) + *schistocytes* on smear

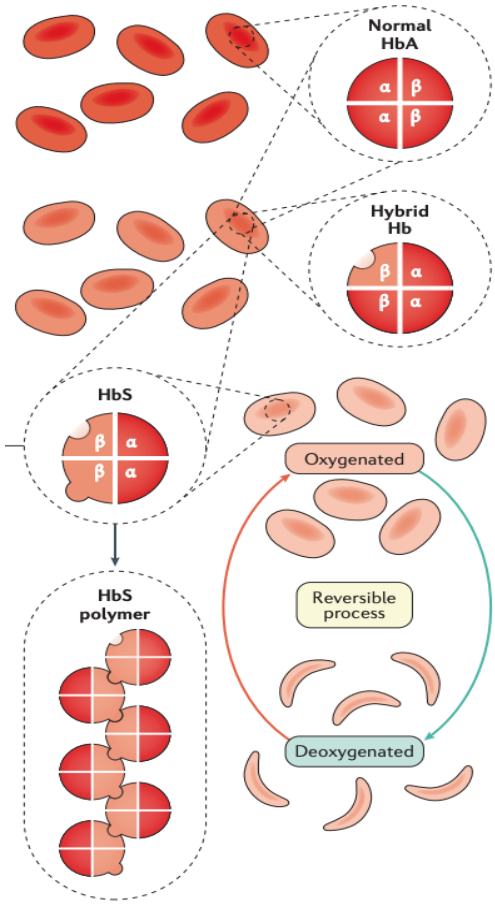
- Microangiopathic: **TTP/HUS, DIC, HELLP, malignancy-associated** (intravascular tumor emboli or DIC; esp. in metastatic mucinous CA), malignant HTN, pulmonary HTN, cavernous hemangiomas of liver, vasculitides (GPA, GCA), scleroderma renal crisis, Kasabach-Merritt
- Macroangiopathic: **heart valve** (prosthetic valve "waring blender", valvular dz, HOCM), **mechanical** (CVVH, ECMO, Impella, LVAD, IABP, TIPS), foot strike (RBC trauma in vessels of feet; "march hemoglobinuria" & "runner's macrocytosis")

Hemolysis from Infectious and Chemical Agents

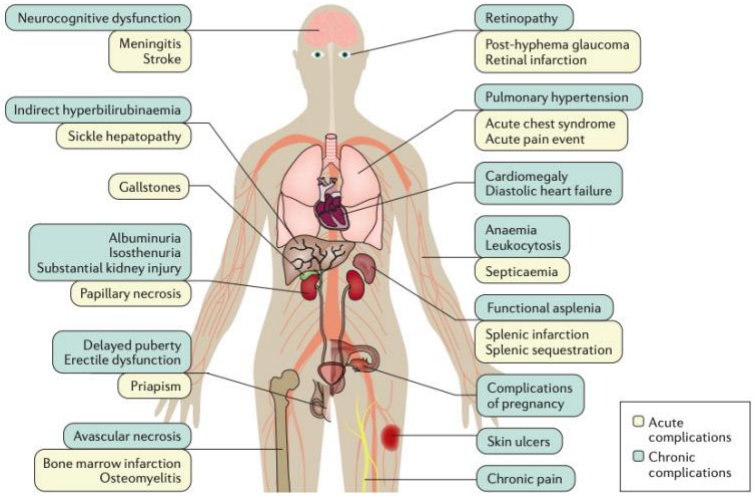
- Babesiosis: "Nantucket fever"; tick-borne parasite → RBC lysis; **clinical manifestations**: ~3 wk incubation → malaise, anorexia, fatigue, f/c, muscle & joint pains; ↑AST/ALT, ↓plts; **Dx**: thin smear, PCR (if neg. smear due to low level parasitemia); can be acquired via RBC transfusion
- Malaria: parasites from mosquitos; parasitized RBCs destroyed in spleen; **clinical manifestations**: febrile paroxysms, rigors, HA, abd. pain, n/v, fatigue; severe hemolysis → hemoglobinuria ("blackwater fever"); **Dx**: +rapid detection test, thin smear, or PCR
- Clostridium perfringens: toxin reacts w/ RBC lipids; cholecystitis, septic abortion w/ severe hemolysis
- Other infections: Bartonellosis (Oroya fever), H. flu, visceral leishmaniasis (kala-azar)
- Chemical or physical agents: **lead**: acute hemolysis or sideroblastic anemia if chronic; Sx: abd. pain ("lead colic"), joint pain, HA, confusion, seizures, ↑ blood lead level; **others**: arsenic, copper, bee and wasp stings, scorpion bite, brown recluse bite, burns

Hemoglobinopathies: Sickle Cell Disorders (NEJM 2017:376:1561):

- **Definitions:**
  - *Sickle Cell Allele*: missense A>T (Glu6Val) mutation in β globin gene (autosomal recessive).
  - *Sickle Cell Trait (SCT)*: heterozygous for β^S globin w/o aberrancy in partnered β globin gene.
  - *Sickle Cell Dz (SCD)*: any inherited hemoglobinopathy w/ formation of Hemoglobin S (HbS) → sickle shape of RBCs.
  - *Sickle Cell Anemia (SCA):* homozygous for β^S globin.
- **Epidemiology:** ~300,000 infants born w/ SCA per year worldwide. ~90,000 to 100,000 w/ SCD in U.S, 1,200 families in Boston area. ~2-3 mill worldwide, primarily in malaria endemic countries.
- **Dz modifiers:** even with same mutation, SCD affected by genetic modifiers, HbF expression levels (HPFH SNPs), environmental (altitude).
- **Pathophysiology:** HbS polymerizes in deoxygenated form (hydrophobic interactions with mutant valine) → rope-like fibers and the classic sickle shape RBCs. Sickling impacts RBC membrane integrity & adheres to vascular endothelium → vaso-occlusive events, particularly small capillary beds w/ potential to affect any organ.



- **Clinical Manifestations & Complications:** Most severe in SCA, intermediate for SC, or S/Thal dz:



  - Acute pain episodes: Sx: fevers, swelling, tenderness, HTN, N/V. Frequency peaks at age 19-39. Higher risk when Hb > 8.5 g/dL and ↓ HbF levels. Triggered by low humidity, dehydration, infection, psychosocial stressors, menses, alcohol, though many w/o clear etiology. Lasts 2-7 days on average. Tx: (1) pain ctrl: opioids +/- NSAIDs; check Acute Care Plan; utilize EPIC order set; if unknown prior dose: IV morphine 0.1-0.15mg/g (max 10mg) or Dilaudid 0.02-0.05 mg/kg (max 1.5mg) → PCA; (2) O2 if <92%; (3) IVF if hypovol.; (4) incent. spirometry (↓ acute chest (NEJM 1995:333:699))
  - Acute Chest Syndrome: 2nd most common cause of hospitalization. Pulmonary arterial circulation has low O2 tension → ↑ risk vaso-occlusion. ACS comprises different pulmonary complications of SCA, including PNA, thromboses, and fat embolism from BM infarction. Defined as presence of infiltrate on imaging + pulm symptoms. *Sx:* cough, SOB, CP, fever. Dx: CXR with pulm infiltrate, fever, ACS Sx, ↑WBC; fall in Hgb or plts can precede imaging findings; need to r/o PE, ACS, PNA; *Tx:* **O2** if <92%, **transfusions** (goal Hb >10; simple, or exchange if severe), **pain control** (see above), **Abx** (CTX/azithro or FQ), **bronchodilators.** NB: 50% preceded by, or associated with acute pain episodes
  - Cardiac: Major cause of death, hemosiderosis induced cardiomyopathy, ↑ MI
  - Neurologic: 25% of pts experience a stroke by age 45; many have silent ischemic lesion(s) leading to neurocognitive impairment over time. Epilepsy 2-3x more common in SCA
  - Hepatobiliary: acute hepatic ischemic, iron overload, pigmented gallstones
  - Bone: ↑ rate of vit. D deficiency and osteoporosis. Osteonecrosis d/t infarction of bone and trabeculae also possible
  - Hyperhemolytic episodes: rare complication (1%); pain, fever, worsening anemia w/in 7-15 days of transfusion, dropping reticulocyte count, DAT may be negative. *Tx:* notify blood bank, hydration +/- steroids, IVIG, rituximab, eculizumab
  - Infection: aplastic anemia w/ parvo B19
  - Splenic sequestration: 20% of pts; ↑ risk of encapsulated infxn
  - Others: hand-foot syndrome, renal pap. necrosis, priapism. Dactylitis seen in 40% of pts

- **Diagnostics:** Hb electrophoresis and High Performance Liquid Chromatography (HPLC) to separate HbS from other variants (HbA, HbF). HPLC ↑ sensitivity and specificity.
  - *Work-up on initial admission:* CBC w/ diff (chronic anemia Hb 8-10, MCV higher end of nml), BMP, LFTs (↑ unconjug. bili), PTT/PT/INR, hemolysis labs w/ LDH, haptoglobin, reticulocyte index (often 3-15%); BCx x2, UA, UCx; CXR to evaluate acute chest syndrome; special slide (polychromasia, sickle cells, Howell-Jolly bodies)
- **Management: VTE ppx, pain control, O2, and incent. spirometry**. IVF, abx, and transfusions as appropriate. **Consult Hematology** for every admission → **SCD pager 28439** for acute issues (acute chest, stroke, etc.) and to consolidate pain mgmt plan before discharge.
  - *Neutral language*: Provider misperceptions of pain interfere with optimal mgmt. Biased language a/w less aggressive pain ctrl and more negative attitudes toward pts (Gen Intern Med 2018;33:685)
  - *Transfusions*: dilute HbS, suppress EPO, improve O2 sats. Goal Hb >10. Indicated in acute stroke, multiorgan failure, acute chest, sequestration, and peri-op. No e/o benefit in acute pain episodes. **Exchange > simple** d/t risk of hyperviscosity. Transfusions should be judicious (ASH guideline) (Blood Adv 2020;4:327). Transfusion ppx: regularly scheduled transfusions reserved for pts w/ > 2 episodes of mod. to very severe acute chest in past 24 mo. despite hydroxyurea; ↓ risk of periop complications w/ pre-op transfusion. Risk of iron overload: (200-250mg of elemental iron/1U

pRBC), 3 iron chelators available: deferoxamine (daily injections, slow), deferiprone and deferasirox (PO but a/w multiple adverse effects).
- *Outpt Tx*: hydroxyurea (↑ HbF; continue inpt), folate & MVI, vaccines for encapsulated bacteria (Mening, HiB, Pneumo), HBV & flu.
- *Allogeneic BMT*: only curative option but multiple possible complications.
- *New pharmacologic approaches*: L-glutamine (↓ oxidative stress in RBCs NEJM 2018;379:226), voxelotor (inhibits HbS polymerization; HOPE trial NEJM 2019;381:509), crizanlizumab (P-selectin antagonist, ↓ RBC adhesion (NEJM 2017;376:429)
- *Gene therapy & editing*: Lentiglobin T87Q β-globin gene therapy vector. BCL11A shRNA. CRISPR for BCL11A erythroid enhancer.

RBC Membrane Defects

- Hereditary spherocytosis**:** RBC membrane protein (ankyrin, spectrin) defect; impaired vertical interactions b/w cytoskeleton and membrane → *osmotically fragile spherocytes*; impeded passage through spleen → *chronic hemolysis*; **complications:** bilirubin gallstones, hemolytic crises (viral), aplastic crisis (parvo B19); **Dx:** +FHx, spherocytes, ↑MCH (>36), EMA binding (↓) or fragility test (glycerol lysis, cryohemolysis, hypotonic salt); **Tx:** splenectomy is curative
- Hereditary elliptocytosis: similar to HS except protein defect affects horizontal interactions → elliptocytes; 90% w/ mild hemolysis; *severity ≠ % ellip. cells on smear*; splenectomy is not routine
- Spur cell anemia: acanthocytes (↑ cholesterol in RBC membrane) in advanced cirrhosis → rapidly progressive hemolytic anemia; usually not significant, but can aggravate pre-existing anemia

RBC Enzyme Defects

- G6PD deficiency***:*** X-linked defic. of G6PD (generates NADPH); *oxidative stress* → hemolysis; **clinical manifestations**: acute hemolytic episode 1-3d after oxidative stress (↓in Hb 3-4g/dL); dark urine, abd/back pain in severe cases; **precipitants:** *meds* (dapsone, nitrofurantoin, primaquine, methylene blue, rasburicase, quinolones, etc.), *foods* (fava beans), *infxn*; **Dx**: ± Heinz bodies on smear; screening test for NADP reductase (fluorescent spot, metHb reduct.); if positive confirm with quantitative test***; testing may be normal in acute hemolytic episode*** (RBCs with lowest G6PD level have hemolyzed), so if normal, repeat in 3mo.; **Tx**: avoid triggers
- Pyruvate kinase deficiency: autosomal recessive defect in PK → defect in ATP gen. → hemolysis (mechanism unknown); **clinical manifestations**: variable anemia; +FHx, ↓PK activity; **Tx:** splenectomy if severe (not curative but ↓ transfusions)

Paroxysmal Nocturnal Hemoglobinuria

- Pathophysiology: **acquired** defect in HSC → ↓CD55 & CD59 complement inhibitors (GPI-linked proteins) on RBC surface → *complement-mediated hemolysis* (intra >> extravascular)
- Clinical manifestations: fatigue (out of proportion to anemia), *hemoglobinuria* (presenting sx in only 25%), **thrombosis** iatypical locations (splanchnic > cerebral > dermal; from ↑ coag), smooth muscle dystonia (dysphagia, abd. pain, ED; from ↓ NO), pulmonary hypertension (from ↓ NO), renal failure, *pancytopenia* (some with AA/MDS)
- Dx: **DAT-**, **flow cytometry** for CD55/CD59 on RBCs & PMNs (clone size underestimated w/ RBCs) vs. FLAER for GPI proteins
- Tx: **eculizumab** (blocks MAC formation, so ↓ intra- but not extravascular hemolysis; ↓transfusions, ↑QOL) (Blood 2011;117:6786); **Fe** (IDA from hemoglobinuria); **anticoagulation** if thrombosis (not 1° ppx); **allo-HSCT** is curative, but normal survival with eculizumab

Polycythemia

- Clinical manifestations: **underlying pulmonary dz**: SOB, DOE, cough, hypersomnolence; **hyperviscosity** (rarely): chest pain, abd. pain, myalgias, fatigue, HA, blurred vision**; polycythemia vera**: pruritus after bathing, erythromelalgia, gout, thromboses, early satiety (from splenomegaly)
- Dx: Hb >16.5 (*men*) or >16 (*women*)
- Workup: Epo level (↓ in 1°; ↑ in 2°)
- Primary polycythemia: acquired or inherited mutation in HSC → ↑↑RBCs; **etiologies**: polycythemia vera (myeloproliferative neoplasm), familial/congenital polycythemia
- Secondary polycythemia: appropriate ↑Epo in response to hypoxia, Epo-secreting tumor, or exogenous; **etiologies**: pulm. dz, OSA, smoking, Eisenmenger, high altitude, post-renal transplant, tumor (HCC, RCC, hemangioblastoma, pheo, uterine fibroids), exogenous Epo, testosterone; **workup**: LFTs (HCC), U/A (RBCs for RCC), CXR (pulmonary dz)

LEUKOPENIAS:

Neutropenia (Blood 2014;124:1251; *Williams Hematology* 9th Ed 2015; Ch 65)

- Definition: **ANC <1500**; mild 1000-1500, mod 500-999, severe <500; agranulocytosis <100-200. (*NB* ANC includes PMNs and bands, but not less mature forms)
- Pathophys: ↓**BM production** (congenital, infiltrative, drug w/ BM toxicity, nutritional), **margination** to spleen/vascular endothelium, or **immune destruction** (drug rxn or autoimmune)
- Hx: meds, autoimmune dz (RA→Felty syndrome, SLE), hematologic disorders/malignancy, nutrition, HIV risk factors, infx hx, FHx of immunodeficiency or BM failure syndromes
- Exam: clue to BM reserve (circulating neutrophils only 3% of total pool). **Purulence** suggests PMNs in BM. **Ulcers w/o purulence or gingivitis** suggest ↓BM pool.
- Dx: CBC w/ diff (Δ in other cell lines; ANC trend); HIV and viral hepatitis; B12, folate, copper; rheum labs if clinical signs; ESR/CRP; BMBx if suspect ↓BM reserve to assess cellularity and differentiation arrest.
- Tx: if incidental and adequate BM reserve, monitor. If inadequate reserve and recurrent infx, G-CSF. "Neulasta" and "Udenyca" = long-acting (14d) G-CSF, "Neupogen" and "Granix" = short-acting (daily) G-CSF. If febrile, treat as infx (ANC >500 can often be managed on outpt basis).

Benign Ethnic/Familial Neutropenia

- Inherited neutropenia: African descent, Sephardic Jews, West Indians, Yemenites, Arab Jordanians
- Etiology: Duffy antigen (*ACKR1*) polymorphism (protects against malaria), alters set point for circulating neutrophil count
- Clinical manifestations: ANC usually >1000; **no increased risk of infection**; normal BM reserve

Drug-induced Neutropenia

- Pathophys: **immune-mediated destruction** of circulating neutrophils by drug-dependent or drug-induced antibodies OR **direct toxic effect** on marrow granulocyte precursors
- Clinical manifestations: usually w/in **3-6 months** of drug initiation; immune-mediated more acute (ulcers, sepsis), BM toxicity more insidious and may be found incidentally
- Tx: d/c offending drug (may be difficult to identify) and usually resolves w/in 1-3wks; if febrile, culture, start broad-spectrum Abx, and consider G-CSF

Drugs a/w neutropenia:

Anti-inflammatory:	***Antibiotics:***	***Antimalarials:***	***Cardiovascular Drugs:***
Acetaminophen	Cephalosporins	Chloroquine	ACE inhibitors
Gold salts	Chloramphenicol	Dapsone	Antiarrhythmics
NSAIDS	Isoniazid	Quinine	Digoxin
Sulfasalazine	Macrolides		Propranolol
	Penicillins	***Antivirals:***	Ticlopidine
Anticonvulsants:	Rifampin	Acyclovir	
Carbamazepine	Sulfonamides (e.g. TMP-SMX)	Ganciclovir	***Psychiatric:***
Phenytoin	Tetracyclines	Oseltamivir	Chlordiazepoxide
Valproic acid	Vancomycin		Chlorpromazine
		Antifungals:	Clozapine*
Antithyroid Drugs:		Amphotericin B	TCAs
Methimazole*	***H2 blockers:***	Flucytosine	
Propylthiouracil*	Cimetidine		
		Diuretics:	Allopurinol
		Thiazides	
		Acetazolamide	
		Furosemide	
		Spironolactone	

*Have formal recommended screening protocols per FDA or expert organization

Congenital Neutropenia

- Definition: neutropenia starting at/around birth; due to primary BM failure of the myeloid lineage
- Clinical manifestations: may have monocytosis accompanying neutropenia; oropharyngeal, respiratory, & skin infx (staph and strep), oral ulcers, gingivitis; some have dysmorphic features

Congenital neutropenia syndromes:

Disorder	Features
Severe congenital neutropenia	Recurrent, severe infx in infancy; risk of AML. Multiple genes and inheritance patterns: *ELANE* (AD) most common. Tx: G-CSF, consider BMT.
Schwachman-Diamond	Bone abnormalities, pancreatic insufficiency, moderate neutropenia. Risk of BM failure, MDS, AML. Ribosome/mitosis defects, most AR inheritance.
WHIM syndrome	Warts, Hypogammaglobulinemia, Infx, Myelokathexis (retention of neutrophils in BM). *CXCR4* mutation (AD).
MonoMAC syndrome	Severe monocytopenia <200, infx risk (e.g. NTB mycobacterium like MAC, fungi), mild chronic neutropenia w/ low B and NK cells. *GATA2* mutation (AD).
Chediak-Higashi	Oculocutaneous albinism, peripheral neuropathy, HLH risk, Plt dysfnx/ bleeding. Neutrophils w/ large granules. Defective lysosome trafficking: *LYST* (AR)
Glycogen storage 1b	Von Gierke's. Hypoglycemia, HSM, seizures, FTT, neutropenia/functional neutropenia, infx. G6P-ase deficiency (AR)
Cyclic neutropenia	Defect in HSC regulation; episodes of severe neutropenia q21 days for 3-6d w/ fever, infx, ulcers. *ELANE* mutations (AD). Tx w/ G-CSF.
Congenital immunodeficiencies	Seen in X-linked agammaglobulinemia, CVID, X-linked hyper-IgM, reticular dysgenesis

Lymphocytopenia (*Williams Hematology* 9th Ed 2015; Ch 79)

- Definition: **ALC <1000**; usually due to ↓in CD4 cells
- Dx: if not obvious from history & meds, check HIV, measure subpopulations and Ig levels

Etiologies of lymphocytopenia:

Infection	HIV, SARS/COVID, WNV, hepatitis, measles, flu, TB, typhoid, rickettsiosis, ehrlichiosis
Systemic	Autoimmune diseases, lymphoma, carcinomas, sarcoidosis, protein-losing enteropathy
Medications	Steroids, rituximab, alemtuzumab, anti-lymphocyte or -thymocyte globulin (ALG, ATG), chemotherapy
Congenital	SCID (multiple mutations and inheritance patterns), CVID (polygenic), ataxia-telangiectasia (*ATM,* AR), Wiskott-Aldrich (*WAS*, x-linked), thymoma
Other	Radiation, major surgery/stress, thoracic duct drainage, nutritional (EtOH, Zn def.)

LEUKOCYTOSES:

Neutrophilic Leukocytosis (*Williams Hematology* 9th Ed 2015; Ch 65)

- Definition: **ANC >7500**.
- Pathophys: ↑**BM** production or release, **demargination** of peripheral neutrophils (half of circulating neutrophils are marginated, so demargination can rapidly ↑ WBC count x2-3)
- Dx: CBC w/ diff (Δs in other cell lines), peripheral smear (morphology, immature forms), BMP, LFTs, ESR/CRP, coags; C. diff if hospitalized and unexplained
- Associated terminology:
  - Left shift: increase in percentage of band forms, usually with metamyelocytes and myelocytes
  - Leukemoid reaction: WBC >50,000 but not leukemia. Mature neutrophils w/ left shift. Normal maturation, morphology, cytogenetics, polyclonality. ↑ leukocyte alkaline phosphatase (LAP) distinguishes from CML. Etiologies: non-heme cancer, infx, asplenia/hyposplenia, meds. If >100,000, may need leukapheresis to prevent vasoocclusive complications/leukostasis

Etiologies of neutrophilia:

Infection	Often acute bacterial; left shift w/ toxic gran., Döhle bodies, cytoplasmic vacuoles
Inflammation	Acute or chronic. Infarction (e.g. MI), burns, vasculitis, collagen vascular disease, gout, IBD/colitis, hepatitis, myositis, nephritis, pancreatitis, Sweet syndrome (fever, erythematous tender skin papules/plaques, arthralgia, eye involvement)
Medications	Stimulation of BM (ATRA, G-CSF, lithium), demargination (catecholamines), release from BM (glucocorticoids, plerixafor), allergic reaction
Stress	Endogenous catecholamines; exercise, heat stroke, surgery, seizure

Asplenia	Functional or surgical; associated thrombocytosis, Howell-Jolly bodies, nucleated RBCs
Cigarettes	May be due to smoking-related inflammation
Neoplasm	Primary MPN or non-heme malig. (BM mets, nonspecific inflamm, paraneoplastic)

Lymphocytic Leukocytosis (*Williams Hematology* 9th Ed 2015; Ch 79)

- Definition: **ALC >4000**
- Pathophys: ↑ **BM** production, **redistribution** (from BM or 2° lymphoid organs), ↓ **cell death**
- Dx: CBC w/ diff (Δs in other cell lines), peripheral smear (morphology, immature forms); BMP, LFTs, ESR/CRP; **if >30,000** (malignant > reactive), blasts or other morphologies concerning for malignancy, send peripheral flow cytometry

Etiologies of lymphocytosis:

Infection	Mono ("atypical" lymphs; EBV), other viruses (CMV, hepatitis, flu, adeno.); pertussis (toxin blocks movement from blood to LNs), toxoplasmosis, TB
Hypersensitivity	DRESS (rash, fever, LAD, ↑eos, ↓plt, ↑LFTs, atypical lymphs), drug rxns, insect bite
Stress	Trauma, cardiac emergencies, status epilepticus, surgery, sickle cell crisis
Asplenia	Large granular lymphocytes, expansion of NK cells
Neoplasm	Leukemia (CLL, LGL, hairy cell), lymphoma (Sezary, MCL, follicular), thymoma

Monocytic Leukocytosis (*Williams Hematology* 9th Ed 2015; Ch 70)

Etiologies of monocytosis (AMC >500):

Infection	Mycobacterial, subacute bacterial endocarditis, Brucella, Listeria, Rickettsia, Dengue, syphilis, CMV, VZV, flu
Inflammation	Collagen vascular diseases, sarcoidosis, IBD, sprue
Neoplasm	MPN, lymphoma, myeloma, non-hematologic malignancies (20% of cases)
Other	Reactive to neutropenia, chlorpromazine toxicity, EtOH liver disease, severe depression, MI, cardiac bypass surgery

Eosinophilic and Basophilic Leukocytoses (*Williams Hematology* 9th Ed 2015; Ch 62 & 63, **Blood 2015;126:1069**)

Eosinophilia:

- Definitions: **AEC >500**; hypereos. >1500; **hypereos. synd. (HES)**: >1500 + tissue damage
- HES: primary (clonal), secondary (reactive), or idiopathic
- Hx: meds, exposures (travel, occupation), FHx, full ROS to assess for organ involvement
- If >1500: CBC w/ diff, smear; end-organ: BMP, UA, LFTs, CK, trop, EKG, PFTs, CXR, pan-CT; tryptase, B12, strongyloides serology; other infx w/u + stool O&P per exposures; ANCA if ?EGPA; serum Ig, peripheral flow if ?MPN
- Tx: If >100K w/ leukostasis s/sx, potentially life-threatening (cardiac damage, thromboemboli, resp failure) → **high-dose steroids** (1 mg/kg pred to 1 g methylpred if severe) + ivermectin if potential Strongyloides; 2nd-line: imatinib (if *PDGFR*+), cyclophosphamide (if vasculitis), high-dose hydroxyurea, IFN-α, vincristine, mepolizumab (anti-IL-5, **NEJM 2008;358:1215**)

Etiologies of eosinophilia:

Etiology	Features
Parasites	Strongyloides, toxocariasis, trichinellosis, hookworm, filariasis, schistosomiasis, ascaris
Non-parasite infections	Aspergillus (ABPA), coccidiomycosis, TB; rarely viral (HIV, HTLV)
Allergic diseases	Asthma, allergic rhinitis, chronic rhinosinusitis, atopic dermatitis, ABPA, episodic angioedema (Gleich syndrome)
Drug reactions	DRESS (2-6w → fever, malaise, LAD, rash, ↑LFTs, AIN); hypersensitivity vasculitis, eosinophilia-myalgia (L-tryp), asymptomatic eosinophilia
Collagen-vascular disease	EGPA (asthma, rhinosinusitis, ANCA vasc.), RA, eosinophilic fasciitis, PAN, IgG4-related diseases, ulcerative colitis
Neoplasm	MPN (often *PDGFRA*-assoc; leukemia, mastocytosis), lymphoma, Sezary syndrome; adenocarcinoma of GI tract, lung; oral squamous cell carcinoma
Others	Adrenal insufficiency, cholesterol emboli (livedo reticularis, purple toes, AKI)

Basophilia: ABC >150

- Etiologies: neoplasm (CML, other MPN, HL), allergy/inflammatory (IBD, chronic sinusitis, JRA), endocrinopathy (DM, hypothyroidism), infection (VZV, flu, TB), ionizing radiation, iron deficiency

MULTILINEAGE CYTOPENIAS:

Pancytopenia (Blood Rev 2018;32:361)

- Definition: reduction in all 3 cell lines (Hgb<12 for women, <13 for men; ANC<1800; platelets <150K)
- Pathophys: **BM infiltration/replacement** (heme malignancy, mets, myelofibrosis, infx [military TB, fungal]), **BM aplasia** (nutritional, aplastic anemia/PNH, infx [HIV, viral hepatitis, EBV, parvo B19], immune destruction, HLH, meds), **destruction** (DIC, TTP, MDS), **sequestration** (hypersplenism: cirrhosis, lymphoma, LGL, autoimmune dz [SLE, RA/Felty], storage diseases)
- Initial Dx: CBC w/ diff, smear, retics, PTT/PT/INR, iron studies, BMP, LFTs, ESR/CRP, LDH, uric acid
- Additional: copper, zinc, folate, B12, HIV, HBV/HCV, EBV, CMV, parvo, ANA, RF, SPEP, BMBx, flow cytometry, abdominal U/S + doppler

- **Infectious Causes of Pancytopenia:**
  - Mechanism: BM failure (usually viral), BM infiltration (military TB, fungal infection), acquired HLH
  - HIV: lymphopenia ± atypical lymphs → pancytopenia; can resemble MDS
  - Hepatitis-associated aplastic anemia (HAA): preferentially affects young men 2-3 mo. post-hepatitis; no association with specific viruse or with drugs/toxins; seen in 2-5% of all cases.
  - Others: HAV/HBV/HCV, EBV, CMV, HHV-6, parvovirus, TB, leptospirosis, dengue, leishmaniasis

Medications that cause Pancytopenia:

Class of Medications	Examples
Anti-gout	Allopurinol, colchicine
Antimicrobials	Chloramphenicol, streptomycin, tetracycline, methicillin, mebendazole, sulfonamides, flucytosine, cidofovir, foscarnet, ganciclovir, linezolid, quinine, quinidine, zidovudine
Anticonvulsants	Phenytoin/fosphenytoin, carbamazepine, levetiracetam, phenobarbital, valproate
Diabetes medications	Sulfonylureas (tolbutamide, chlorpropamide)
Antihistamines	Cimetidine, ranitidine, chlorpheniramine
Thyroid medications	Methimazole, methylthiouracil, propylthiouracil
Cardiovascular	Amiodarone, captopril, lisinopril, nifedipine
Diuretics	Furosemide, thiazides, acetazolamide, methazolamide
Immunosuppressant/ rheumatologic	Azathioprine, MTX, sulfasalazine, mesalamine, penicillamine, leflunomide, mercaptopurine, gold salts
NSAIDs	Indomethacin, ibuprofen, sulindac, aspirin, diclofenac
Psychiatric/sedatives	Chlorpromazine, lithium, prochlorperazine, chlordiazepoxide

* In addition to drugs above, consider cytotoxic chemo, EtOH, benzene, insecticides (DDT), lindane, hydrocarbon-based gluevapors, radiation exposure

- **Nutritional Deficiencies:**
  - Copper: Risks: TPN, GI/bariatric surgery, excessive zinc, renal failure. Dx: low serum Cu and ceruloplasmin; BMBx w/ erythroid + myeloid precursor vacuolization + ringed sideroblasts, often confused with MDS.
  - Folate/B12: can cause pancytopenia along with anemia (additional info in Anemia section).
  - Anorexia nervosa: Can present as pancytopenia or anemia/leukopenia. BMBx w/ gelatinous degeneration. Resolves entirely w/ appropriate nutrition.

- **Autoimmune Diseases a/w Pancytopenia:**
  - Mechanism: often multifactorial; autoimmune destruction, BM suppression, hypersplenism, medications, HLH/MAS (rarely)
  - Etiologies: SLE (most common), Felty's (RA, neutropenia, splenomegaly), RA-associated LGL, sarcoid
  - Tx: treat underlying condition; splenectomy in rare cases of Felty's syndrome

- **Aplastic Anemia (AA) and Bone Marrow Failure Syndromes** (NEJM 2018;379:1643 , NEJM 2017;367:1540:
  - Etiology: congenital or acquired; majority of causes are idiopathic
  - Pathophys: loss of HSCs → BM hypoplasia/aplasia. Mechanisms: autoimmune destruction by T cells, viral infx, direct injury (drugs, chemicals, radiation), clonal/genetic disorders
  - Inherited syndromes: Fanconi anemia (DNA repair defects, most AR), dyskeratosis congenita (telomere maintenance mutations, variable inheritance), Shwachman-Diamond Syndrome (ribosome/mitosis defects, most AR), congenital amegakaryocytic thrombocytopenia (TpoR mutations, AR)
  - PNH association: 2/3 have PNH clones and 30% w/ PNH have preceding AA. Send CD59 flow for all.
  - Dx: BM Bx w/ hypocellular marrow w/o fibrosis or malignant cells. Severe AA = two of ANC <500, plts <20K, & retics <20K; very severe = severe w/ ANC<200.
  - Tx: Age <40-50: allo-HSCT. For HSCT: 1) critical to r/o familial syndrome if related donor, 2) etiology of AA may decrease tolerance of conditioning regimens (e.g. Fanconi anemia), 3) steps are taken to reduce GVHD (BM source, cyclophosphamide, etc.) as typically no need to preserve a GVT effect (see Allogenic SCT section). Age >50y or cannot tolerate HSCT: immunosuppression (ATG + cyclosporine, 2nd-line alemtuzumab [pan-T cell monoclonal antibody]) and eltrombopag (TpoR agonist)

Hemophagocytic Lymphohistiocytosis (HLH)

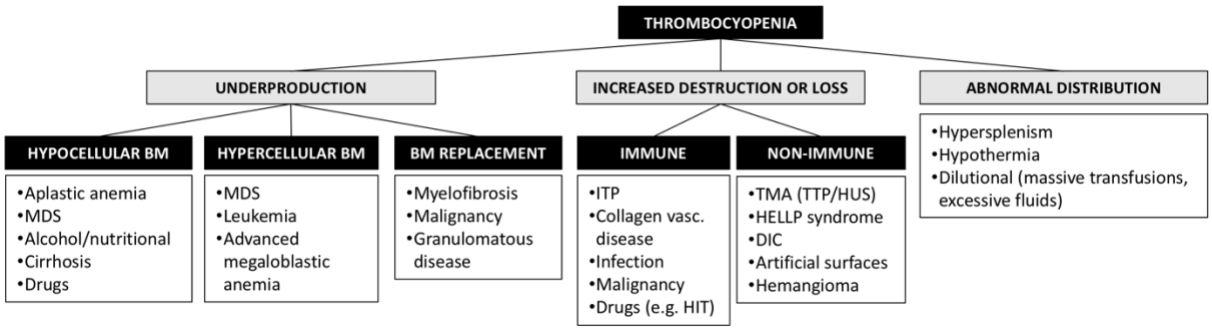
- Pathophys: excessive immune activation. Failure to downregulate activated macrophages due to defective perforin-mediated elimination by NK cells and CD8+ T-cells, leading to high levels of cytokines, particularly IFNγ. Activated macrophages subsequently phagocytize other blood cells (hemophagocytosis). Cytokine storm leads to organ failure and mortality.
- Familial form: up to 25% of cases. Typically presents in childhood, more likely to be episodic. Most commonly due to disabling mutations in perforin-mediated cytotoxicity (AR inheritance).
- Triggers: disrupted immune homeostasis. Either immune-activating (infx [e.g. EBV], autoimmune flare) or cause immunodeficiency (malignancy, HIV, inherited immunodeficiencies).
- Clinical manifestations: splenomegaly, hepatomegaly, LAD, fever, cytopenias, high ferritin, high TGs, elevated LFTs, abnormal coags/fibrinogen/d-dimer, elevated LDH. 1/3 have neurologic sx (seizures, AMS, PRES). 1/3 have rash. Less common: ARDS, hypotension, AKI or hyponatremia, bleeding.
- Macrophage activation syndrome (MAS): form of HLH in the setting of a rheumatologic disorder. May have varied cytokine profile (higher IL-18).

Diagnostic criteria for HLH: 5/8 of the following
1. Fever ≥ 38.5°C (101.3°F)
2. Splenomegaly
3. 2 or more cytopenias: Hgb <9 g/dL (<10 for infants <4 wks), plt <100 K/μL, ANC <1000/μL
4. HyperTG (fasting TG >265 mg/dL) and/or hypofibrinogenemia (<150 mg/dL)
5. Hemophagocytosis in bone marrow, spleen, lymph node, or liver
6. Low or absent NK cell activity (can consider flow for NK perforin or CK107α as proxy)
7. Ferritin >500 ng/mL (though higher more specific)
8. Elevated soluble IL2R (CD25)
H score: ≥250 = 99% and ≤90 = <1% probability of HLH (Arthritis Rheum 2014;66:2613)

- Dx: CBC w/ diff, PT/aPTT, fibrinogen, D-dimer, LDH, ferritin, LFTs, TGs. If high suspicion, IL-2Rα, BMBx, flow cytometry, Ig levels, genetic testing, and TTE/troponin (end-organ toxicity). Infx w/u to rule out mimic/trigger (Cx, serology/PCR of EBV/CMV & other viruses, LP, imaging).
- Tx: (Blood 2015;125:2908)
  - **Untreated HLH is almost always fatal**
  - Tx of relevant underlying triggers are important and can lead to resolution
  - Supportive care for anemia, thrombocytopenia, bleeding, BP control (risk of PRES)
  - Begin HLA typing and donor screening early in case patient should need HSCT
  - HLH directed therapies (HLA-94 protocol): **etoposide & dexamethasone** (Blood 2017;130:2728); **intrathecal MTX and hydrocortisone** if CNS disease; **HSCT** in severe or familial cases or where trigger unable to be resolved timely (malignancy). Neutralizing IFNγ antibodies on horizon (efficacy signal in peds, NEJM 2020;382:1811)

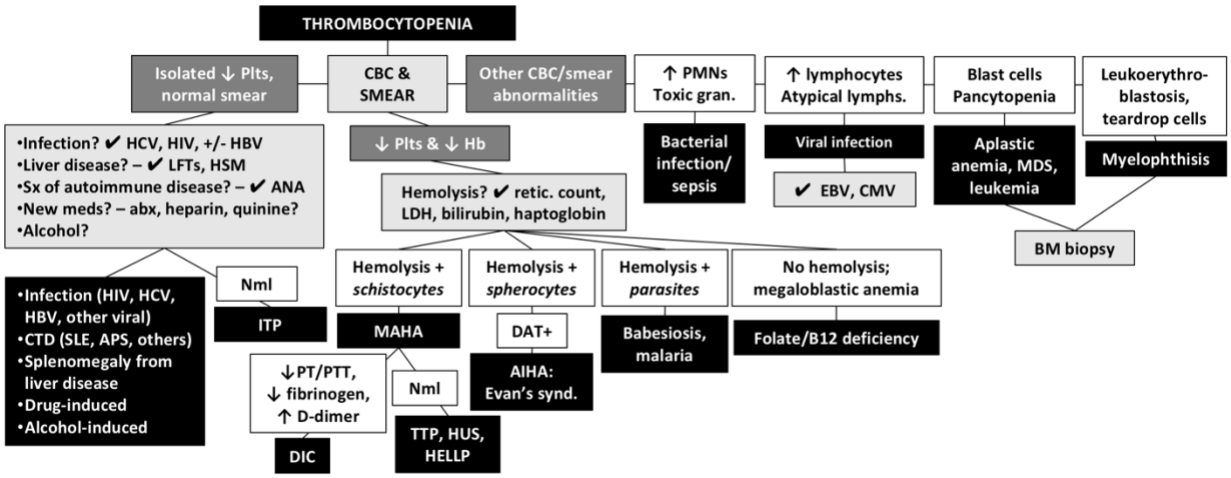
Thrombocytopenia (Mild 100-150K, moderate 50-100K, severe <50K)

- Etiologies: (1) ↓**production**, (2) ↑**destruction/consumption**, (3) **redistribution/sequestration**:



- Manifestations: non-palpable petechiae, often in dependent areas (lower extremities, sacrum), purpura, mucosal bleeding (gingival, epistaxis, menorrhagia, GI bleed)
  - Risk of bleeding: plt count alone is imprecise for estimating bleeding risk; **<100K** w/ major trauma, **<50K** w/ surgery, **<20K** spont. bleed, **<10K** severe bleed
- Hx: infection, HIV/HCV risk, pregnancy, autoimmune diseases, dietary restrictions, EtOH use, meds (**heparin**, abx, chemotherapy, herbal supplements)
- Dx: Rule out pseudothrombocytopenia (e.g. artificial thrombocytopenia d/t plt clumping) w/ repeat citrated CBC and/or smear.
  - CBC w/ diff (other cell lines), smear (*schistos, blasts, megakaryocytes, plt clumping*), coags (help w/ assessing overall bleeding risk and w/u for some etiologies); HIV, HCV (if not ✓recently). Additional testing based on suspected etiology.

Approach to Dx of thrombocytopenia:



Immune Thrombocytopenia (ITP) (Blood 2011;117:4190, ASH Educ Program 2010;1:377)

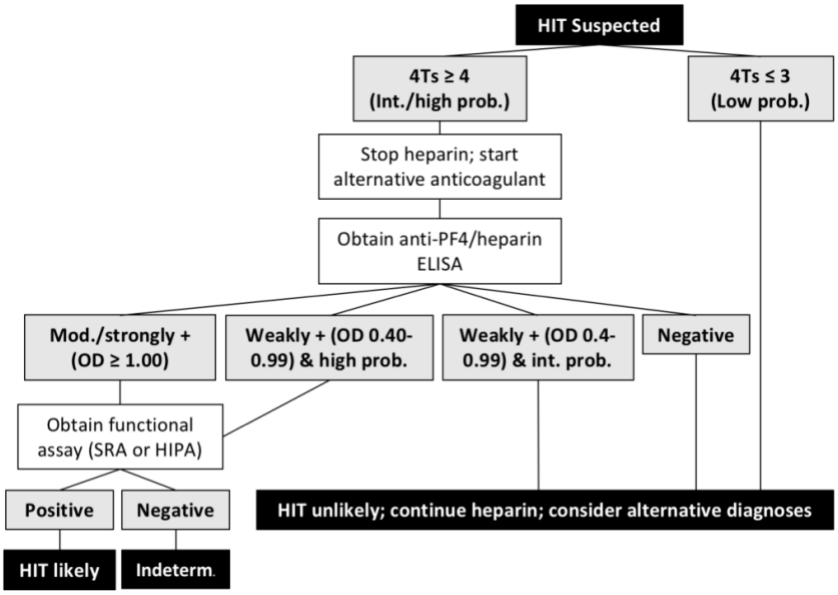
- Pathophys: antibody-mediated platelet destruction; autoantibody binding to megakaryocytes can occur impairing plt production.
- Etiology: primary (80%; no clear associated condition), secondary (e.g., SLE, APLAS, CVID, CLL, Evan's, HCV, HIV, H. Pylori), drug-induced immune thrombocytopenia (DITP; this is distinct from drug-dependent marrow suppression).
- Dx: *Primary ITP*: isolated ↓ plts <100K, normal smear; **dx of exclusion;** BM bx not needed unless atypical. *Secondary ITP*: ✓HIV/HCV +/- H. pylori in all, as indicated HBV, ANA, APLS, TSH, EBV, CMV. *Drug-induced*: Typically abrupt ↓plt within 1-2 weeks. Can happen after a single dose if drug was taken previously/intermittently. Plt recovery begins 1-2 days after cessation, complete by 1 week. Includes HIT (see below); ***List of common offending agents*** (ASH Educ Program 2009;1:153)
- Tx: treat if plts <30K; if 20-30K and no/mild bleeding (skin only), can be observed
- Response to tx: Complete Response = plt >100K on 2 checks 7d apart; Response = plt >30K & >2x↑, no bleeding; No response = plt <30K or <2x↑ or bleeding

	Treatment of ITP:
1st line:	**Steroids** (*dex. 40mg x4d* or pred 1mg/kg x21d + taper) +/- **IVIG** (1g/kg x1-2d PRN) if need rapid ↑; **anti-D** (if Rh+, spleen+) if steroids are contraindicated.
2nd line:	If steroids & IVIG fail: **splenectomy** (wait 6mo; successful in 2/3; ↓ remission w/ age) or **rituximab** (✓HbsAg, anti-HBc; ↓remission vs. splenectomy); If splenectomy/rituximab fail: **TRAs****; Additional options: **danazol** (not in liver disease, women), dapsone, vincristine, azathioprine, cyclophosphamide
Severe bleeding:	**Plts** + **IVIG** (1g/kg x1-2d) + **methylpred** (1g x3d) or **dexamethasone** (40mg x4d) + **romiplostim** 500mcg SC; *if does not respond to plts*: **Amicar** (0.1g/kg/30min then 0.5-1g/hr gtt or similar dose PO) or **tranexamic acid** (IV 1g/10min → 1g q8hrs)

TPO receptor agonists (TRAs): **romiplostim (Lancet 2008; 371:395) (Nplate, Amgen; SC injection qwk; side effects: HA/GI sx) & eltrombopag (Blood 2013;121:537) (Promacta; PO qd; side effects: HA/GI sx, ↑LFTs)

Heparin-Induced Thrombocytopenia (Blood 2017;129:2864, Blood 2012;120:4160, Chest 2012;141:495)

- Pathophysiology: heparin/PF4 complex autoAb → binds, activate plts & monocytes → ↑ thrombin → hypercoag. state w/ thrombosis, ↓ plts (via removal of Ab-coated plts in spleen & consumption)
- Risk factors: >4d; tx > ppx; UFH > LMWH; major surgery (*resets "clock"*); females
- Clinical manifestations: 5-10d after exposure, **>50%**↓ w/ typical **nadir 40-80K**; venous (20-50%) and arterial (10-20%) thrombosis: LE veins, PE, peripheral arteries, CVA, adrenal hemorrhage, skin necrosis at injection site. *Early-onset*: 24hrs; due to Ab from heparin within 1-3mo; *Delayed*: days-wks after heparin d/c'ed
- Dx: **4Ts score** (Blood 2012;120:4160) to determine pre-test probability: low-risk (≤3) has *high NPV* (99%). If intermediate/high risk: **Anti-PF4/heparin ELISA**. If positive: **Serotonin Release Assay (SRA)**



- Tx: **stop heparin**; **start** fondaparinux (stable, non-surg pt), argatroban (renal failure, surg pt; monitor chromogenic Xa [20-40%]), or bivalirudin (PCI, liver failure; monitor diluted thrombin time [dTT]); *no VKA* until plts >150. Will need 4 weeks of anticoagulation if HIT only or 3 months if HIT + thrombosis. (Blood 2012;119:2209)
- Heparin re-exposure: PF4 Abs disappear after median 85 days. Can be re-exposed if Abs cleared. For high-risk procedures (ex. cardiac bypass), can receive heparin intra-op w/ alternative agent post-op.

Secondary Immune Thrombocytopenia

Rheumatologic/Autoimmune Disorders:

- Pathophysiology: Secondary ITP is the major mechanism
- Etiologies:
  - antiphospholipid syndrome: in 20-40%, usually mild; if severe, treat similar to ITP; steroids not effective in most; *no TRAs* (may ↑ thrombosis)

- SLE: in 20-40%, may be presenting sx; usually mild but is a predictor of poor prognosis; if severe, steroids; rituximab if refractory; IVIG if severe bleeding
- other CTDs: polyarteritis nodosa, RA, MCTD, Sjogren syndrome

Infections:

- HIV: Secondary ITP; if develops while on ART**, add AZT**; if *clinically sig. bleeding* or fails AZT, ***IVIG*** (1g/kg), steroids (short-term), or anti-D (if Rh+, spleen+); if refractory, dapsone, danazol
- HCV: Secondary ITP; can also be related to *chronic liver disease*; if *clinically sig. bleeding*, ***IVIG*** (steroids may ↑ viral load); *eltrombopag* may ↑*PVTs in cirrhosis* (**NEJM 2012;367;716**)
- Other viral infections: rubella, mumps, varicella, parvovirus, EBV, CMV, Zika
- H. pylori: controversial, but some evidence (in Japan, Italy; not US, Europe) that eradication ↑plts in ITP; *ASH ITP guidelines:* screen patients w/ ITP for H. pylori and treat if positive (**Blood 2011;117:4190**)
- Bacterial infection/sepsis: bone marrow suppression or consumption (if DIC)
- Other infections: malaria, babesiosis, anaplasmosis, RMSF

Thrombotic Microangiopathies (TMA) (**NEJM 2014;371:654**)

Diverse group of conditions (either aquired or hereditary) defined by macroangiopathic hemolytic anemia (**MAHA**) + ↓**plts** + **organ injury**

Primary TMA: TTP, Shiga toxin-mediated HUS, drug-induced, complement-mediated TMA. Many systemic disorders can present w/ MAHA and thrombocytopenia (distinct from Primary TMA).

- Pathophysiology**:** vascular damage → microvascular thrombosis → consumption of plts, shearing of RBCs (→ **schistocytes**), organ injury due to vascular occlusion (**NEJM 2014;371:654**)
- Dx**:** **MAHA** (↓Hb, ↑LDH, ↓haptoglobin, +schistos, DAT-), ↓**plts**, **nml coags**, +/- ↑**Cr**

TTP: *ADAMTS13 deficiency* (acquired via Ab >> inherited def.) → ultralarge vWF multimers (**Blood 2017;129:2836**)

- Clinical features: fatigue, purpura, GI sx, neuro sx in 2/3 (ranges from minor confusion/HA → FNDs, seizure), fever uncommon, AKI minimal; **classic "pentad" rare**
- Dx: **PLASMIC score** (**Lancet 2017;4:157**):
  - *low:* evaluate for other causes
  - *moderate*: c/s heme, **send ADAMTS13** activity (takes 3-5d). If ADAMTS13 activity <10%, send mixing study/IgG to identify inhibitor
  - *high*: c/s heme, send ADAMTS13, consider **empiric plasma exchange**
  - Tx: **plasma exchange** +/- **steroids** [1mg/kg PO pred]) until remission (nml organ function; plts >150 >2d); if unresponsive or exacerbation, add **rituximab**. Recurrence within 30 days = exacerbation; >30d = relapse (occurs in 40%)

ST-HUS: Shiga toxin (*E. coli* O157:H7, *Shigella*) → endothelial, kidney cell damage; severe abd. pain, n/v, bloody diarrhea, ***severe AKI***; Dx: stool + for organism or toxin; **supportive** tx

Complement-mediated: factor H/I/B, C3, CD46 defect (hereditary or acquired Ab) → uncontrolled alternative complement activation → Membrane attack complex → endothelial, kidney damage

- Clinical features: preceding infection (50%), malaise, poor appetite; *severe AKI*; 20% w/ extra-renal manifestations (CNS, cardiac, pulm. hemorrhage, pancreatitis)
- Dx: genetic screening, autoAb; **may have** ↓**C3/C4**; neg. stool tests
- Tx: supportive care, plasma transfusion/exchange, **eculizumab** (C5 mAb; monitor CH50)

Drug-induced TMA: *immune-mediated* (Ab to plt, neutrophils, endothelails): quinine, quetiapine, gemcitabine; sudden onset f/c, abd pain, n/v/d, AKI; *non-immune* (direct cellular damage): calcineurin inhibitor (e.g., tacro), chemo, VEGF inhib; Sx*:* gradual onset fatigue, HTN. Tx: discontinue offending drug

Other primary TMA syndromes: children >> adults; *metabolism-mediated*: cobalamin C disease; ✓ homocysteine/MMA levels if TTP/HUS/aHUS Dx unrevealing; *coagulation-mediated*: Hereditary deficiency in coagulation proteins

Systemic disorders w/ MAHA, thrombocytopenia: HELLP, severe HTN, infxn/sepsis, malignancies (microvascular metastases), rheumatic disorders (SLE, SSc, APLS), HSCT, DIC, severe B12 deficits

Other Etiologies of Thrombocytopenia

- Chronic liver disease: splenic sequestration due to portal HTN and ↓TPO (synthesized in liver); usually mild-moderate; may have s/sx of chronic liver disease or may be initial manifestation
- Alcohol: usually mild; direct toxic effect +/- nutritional def, if EtOH liver disease then as above
- Nutritional deficiencies: ↓ plt production; low folate, B12, copper; dietary practice, excessive zinc consumption, malabsorption. Usually mild and w/ other defects in hematopoiesis (e.g., megaloblastic anemia)
- BM disorders/suppression: Usually other cytopenias +/- abnormal cell morphologies; Malignancy, MPN, leukemia, MDS or drug-induced (linezolid, daptomycin, valproic acid, gold compounds, chemo, immunosuppression)

Thrombocytosis (ASH Educ Program 2007;1:363)

Defined as Plt >450K. Autonomous <10%, reactive >90% of cases. Often detected incidentally. When incidental, normalizes on its own >90% of the time within 8 mo.

- Etiologies: inflammation/infection (acute or chronic), acute blood loss, recovery from thrombocytopenia, iron deficiency, postsplenectomy, malignancies (CML, PV, myelofibrosis, MDS, AML, ET), drugs, hemolytic anemia
- Clinical manifestations: usually asymptomatic; may have vasomotor symptoms (HA, visual symptoms, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia), bleeding symptoms >> thrombotic events (suspected due to acquired vWF deficiency)
- Dx: iron studies, smear, JAK2/CALR/MPL to evaluate for MPN
- Tx: treat underlying etiology; baby aspirin effective for vasomotor symptoms

Qualitative Platelet Disorders

Defects in platelet receptors for adhesion and ligand binding, or signal transduction pathways. Can be part of a genetic syndrome.

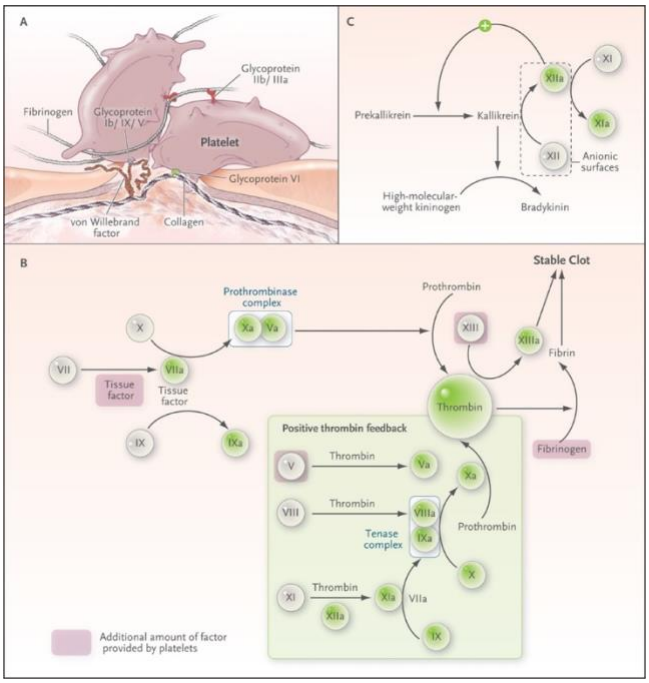
Hereditary:

- Von Willebrand's disease: deficient/defective vWF; mucosal bleeding, menorrhagia; nml/ ↑ PTT, ↓vWF antigen/activity, ↓factor VIII activity; **DDAVP** (intranasal or IV 0.3μg/kg), **amicar/TXA**
- Glanzmann's thrombasthenia: auto. recessive absence of GPIIb/IIIa receptor; bleeding, **nml plts**
- Bernard-Soulier: auto. recessive absence of Gp Ib-IX-V receptor; bleeding, ↓ **plts**
- Platelet storage pool disorders: autosomal dominant defect in plt granules.; bleeding, **nml plts**
- Wiskott-Aldrich: X-linked rec. immunodeficiency, abnml & ↓ **plts**; bleeding, infxn, eczema

Acquired:

- Medications: NSAIDS, P2Y12 antag., PCNs, heparin, dipyridamole, cilostazol, nitrates, CCBs
- Uremia: defective adhesion and activation; improved w/ dialysis, **DDAVP**, estrogens
- Acquired VWD: dysproteinemias (MGUS, MM, WM); AoV disease (i.e. Heyde's syndrome)
- Others: myeloproliferative disorders, cardiopulmonary bypass, trauma

Overview



- Primary hemostasis: initial steps in clot formation relying on fidelity of vessel wall and interactions between vessel wall, platelets, and von Willebrand factor (vWF)
- Secondary hemostasis: formation of fibrin-based clot relying on coagulation factors
- Disorders of 1^0 hemostasis often p/w mucocutaneous bleeding or petechiae; whereas, disorders of 2^0 hemostasis p/w deep tissue bleeding or hemarthroses. vWF deficiency may present with both
- VTE refers to venous thromboembolism (e.g. DVT, PE).
- Hypercoagulable state or thrombophilia refers to an acquired or inherited tendency to thrombosis

Approach to Suspected Bleeding Disorders

- Underlying conditions: cirrhosis, renal disease, cancer, connective tissue disorders (e.g. EDS), HHT
- History: family history, bleeding during infancy (umbilical stump, deciduous teeth loss), menstrual history, anemia, trauma, surgeries, procedures, pregnancy, malabsorption
- Medications: anticoagulants and drugs affecting their metabolism (e.g. CYP3A4, p-glycoprotein, vitamin K). *NB: DOACs can cause abnormal coags*
- Exam: cutaneous (petechiae, bruising, telangiectasias [HHT], hair follicles [scurvy], albinism [rare platelet disorders]), splenomegaly, joint laxity (CTD), cardiac murmurs (aortic stenosis), macroglossia/organ infiltration (amyloid)
- Laboratory evaluation of 1^o hemostasis:
  - CBC to look for thrombocytopenia, citrated tube will prevent pseudothrombocytopenia
  - vWD Panel (see below), platelet function (e.g. platelet aggregation assays, PFA-100)
  - Rare: electron microscopy, genetic testing
- Laboratory evaluation of 2^0 hemostasis:
  - PT/INR and PTT: standard initial tests
  - Thrombin time (TT)/reptilase time (RT): final step in clotting cascade (fibrinogen to fibrin)
  - Mixing studies: Patient plasma and normal pooled plasma are mixed. Measure the clotting time that was initially prolonged.
    - Clotting time corrects: factor deficiency
    - Clotting time does not correct: circulating factor inhibitor
  - Specific factor/inhibitor assays

Interpretation of PT and aPTT

Prolonged aPTT, normal PT

- If mixing study correct, perform assays for factors (e.g., XII, XI, IX, VIII). If mixing study does not correct, suspect acquired factor inhibitor, but also check lupus anticoagulant (hypercoagulable state) and factor VIII activity (rare acquired hemophilia A)
- Subtypes of vWD can prolong PTT due to low factor VIII activity
- Hemophilia A (Factor VIII deficiency) is most common inherited factor deficiency, followed by hemophilia B (Factor IX deficiency). Factor XI deficiency is autosomal dominant, often seen in Askhenazi
- Some malignancies like plasma cell neoplasms can produce heparin-like substances
- Deficiency of Factor XII, prekallikrein, and high molecular weight kinogen (HMWK) not associated with bleeding diathesis

Prolonged PT, normal aPTT

- Mixing study to look for factor VII deficiency/inhibitor
- Look for systemic issues like vitamin K deficiency, liver disease, warfarin, DIC

Prolonged PT and aPTT

- May involve common pathway defects but should also consider combination of etiologies above
- Congenital deficiency of common pathway factors are rare
- Consider acquired factor X deficiency from amyloidosis and acquired inhibitors to X/V/II/I
- Vitamin K deficiency or significant vitamin K antagonist use

- Liver disease and DIC

Suspected bleeding disorder but normal PT and aPTT

- Further evalute for vWD, other platelet disorders (e.g, Glanzmann, Bernard-Soulier, Chediak-Higashi), factor XIII deficiency/inhibitor, chromogenic factor VIII assay, vitamin C deficiency, and assess for other systemic conditions above.

Hemophilia

- X-linked bleeding disorder characterized by deficiency/complete lack of factor VIII (A) or factor IX (B)
- Patients are prone to bleeding, and can develop joint degeneration from recurrent hemarthoses
- Therapy starts in childhood, adults often managed by pediatric hematology (**J Blood Med 2010;1:183**)
- Tx: is factor replacement (concentrates from plasma, recombinant, and products with extended half-life). Tx strategies include:
  - On-demand (when bleeding occurs)
  - Standard PPX (used in severe cases where factor level <1%) and started after first bleed or at 2 years old, whichever is earliest
  - Complications include development of factor inhibitors → bleeding, can ↓ w/ *emicizumab* (humanized monoclonal Ab that activates Factor V) (**NEJM 2017;377:809**)
  - Investigational therapies include additional half-life extension via recombinant products, gene therapy, cellular therapies (introducing intact cells with gene for factor), concizumab (anti-TFP1)

Von Willebrand Disease

- Most common bleeding disorder, affecting up to 1% of the population. Aids in clot formation by stabilizing factor VIII (giving it a longer half-life) as well as binding platelets and endothelial components to form a bridge.
- Lab Tests: VWF Ag, VWF activity, factor VIII activity. If any of these three are abnormal, further testing for type includes VWF multimer distribution and ristocetin-induced platelet aggregation (RIPA).
  - Type 1: *Quantitative deficiency* in VWF, 75% of all patients. Presentation is mild to severe based on degree of deficiency.
  - Type 2: *Qualitative defect* in VWF.
    - 2A: Decreased vWF-dependent platelet adhesion, deficiency of high-molecular weight (HMW) multimers
    - 2B: Increased binding affinity of VWF for platelets (GP1bα)
    - 2M: Decreased vWF-dependent platelet adhesions with normal multimers
    - 2N: Decreased vWF binding affinity for factor VIII
  - Type 3: Rare. Marked decrease or absence in vWF due to mutations in mRNA expression. Presentation is severe with mucocutaneous bleeding as well as soft tissue and joint bleeding (due to loss of FVIII)

VWD type	Frequency (% of VWD)	Bleeding phenotype	Genetic inheritance	Response to DDAVP	First line VWF assays	Second line VWF assays	Genotyping
1	70	Mild to moderately severe	Autosomal dominant	Good	VWF activity < 0.35 IU/dL; Activity to Ag ratio ≥0.7; VWF:CB normal; VWF:CB to Ag ratio ≥0.7	High RIPA variable decreased or normal; VWF multimers for equivocal cases, all MWM present	Not indicated
2A	10–15	Moderate to moderately severe	Autosomal dominant or recessive	Mild to moderate	Activity to Ag ratio <0.7; VWF:CB to Ag ratio <0.7	High RIPA decreased; high & intermediate MWM missing	Exons 20–27
2B	<5	Moderate to moderately severe	Autosomal dominant	Not indicated	Activity to Ag ratio <0.7; VWF:CB to Ag ratio <0.7	Low RIPA increased, high RIPA decreased; high MWM usually missing	Exon 28
2M	<10	Significant	Autosomal dominant	Mild to moderate	Activity to Ag ratio <0.7; VWF:CB normal; VWF:CB to Ag ratio ≥0.7	High RIPA decreased; all MWM present	Exons 29–52
2N	Uncommon	Mild to moderate	Autosomal recessive	Suboptimal	Activity to Ag ratio <0.7; VWF:CB normal; VWF:CB to Ag ratio ≥0.7	VWF:FVIIIB decreased; all MWM present	Promoter
3	Rare, but high in Scandinavia	Severe	Autosomal recessive	No response	Virtually absent VWF	Virtually absent VWF	Whole gene

CB, collagen binding; DDAVP, desamino-8-arginine vasopressin; MWM, molecular weight multimers; RIPA, ristocetin-induced platelet aggregation; VWF, von Willebrand factor; VWF:FVIIIB, VWF-factor VIII binding.

- Management:
  - Desmopressin (DDAVP): Promotes release of VWF. IV dosing often given prior to a procedure (onset within 60 minutes, effect lasts at least 6 hours) (**Lancet 1977;1:869**). Intranasal dosing can be used for less serious bleeding or by women during menses to prevent heavy flow. Test doses are often given prior to the first-time use
  - VWF replacement: Multiple preparations exist. Used during large bleeding episodes in severe cases
  - Aminocaproic acid and transexamic acid: Decreases fibrinolysis, preventing dissolution of a hemostatic plug. Can be used in conjunction with DDAVP for mild cases

Approach to Suspected Hypercoagulability

- *1st unprovoked VTE:* Typically, no need to test as inherited thrombophilic abnormality does *NOT* significantly ↑ risk of recurrent VTE in this group
- *DO NOT* test at time of event. If performed, should be *2 weeks minimum following discontinuation of AC* to avoid repeated testing ($$$), confounded results, and recurrent visits
- When determining duration of AC, assess whether any provoking factors are chronic or transient:
  - Recent surgery/trauma, immobility, hospitalizations, infections
  - Review age, personal history of prior VTE, family history, obstetric history, ROS for malignancy (only *age-appropriate* screening) and systemic disease (IBD, infection, SLE, nephrotic, MPN, etc)
  - Check med list: OCP, HRT, antiphospholipid-inducing (e.g., hydralazine, procainamide)
- Candidates for testing:
  - Patients with VTE and 1st degree releative with VTE prior to age 45
  - Young patients (<45 yo) with VTE
  - Recurrent thrombosis
  - Arterial thrombosis: APLAS testing
  - Clot in portal, hepatic, splenic, renal, mensenteric, or ceberebral venous thrombosis: consider APLAS, JAK2 (MPN), and flow cytometry for CD55/59 (PNH)
- Homocysteine and MTHFR mutational analysis should **NOT** be performed

Factor V Leiden

- Factor V Leiden (FVL) is a mutant form of factor V resistant to protein-C mediated cleavage
- Epidemiology: Most common inherited thrombophilia. 99% are heterozygotes: odds ratio for VTE of about 4. Homozygotes have an OR of about 12 for VTE (**JAMA 1997;277:1305**, **Eur J Epidemiol 2013;28:621**)
- Testing: *activated protein C resistance functional assay* (heparin products may interfere)
  - Will reflex to genetic testing, which is unaffected by current AC
- Patients with FVL generally only require anticoagulation if they develop a DVT or if they have a high-risk situation such as surgery or pregnancy
- Tx: Anticoagulation for provoked VTE is usually 3-6 mo. and may continue indefinitely based on lack of other provoking factor, famhx of VTE, recurrent thrombosis, life-threatening thrombosis, thrombosis at unusual site, or >1 inherited prothrombotic defect

Prothrombin G20210A mutation

- Epidemiology: Second most common thrombophilia. Occurs with one nucleotide substitution (G->A at position 20210), which leads to 30% more prothrombin (factor II)
- Testing: *genetic testing* (not affected by current AC)
- Odds ratio for VTE is about 3-4 compared to the general population. However, if a patient has both FVL and Prothrombin G20210A mutation, which is not uncommon*, their OR is approximately 20*.
- Tx: Anticoagulation considerations are similar to FVL

Protein C and S deficiency

- Pathophys: Activated protein C/S inactivate Va and VIIIa. Both are relatively uncommon (**Blood 1998;92:2353**, **Thromb Res 2015;135:923**). Can be d/t ↓level or function
- Testing: free protein C functional assay and antigen assays for protein C and S
  - ↓ by acute thrombosis, VKA, liver disease, DIC, chemo, uremia (PC), pregnancy, OCP, nephrotic syndrome (PS)
  - ↑ by DOACs. HLD and nephrotic syndrome for PC
- OR of VTE is 7.5 for Protein C deficiency and 5.4 for Protein S deficiency.
- Dx of either deficiency is impossible during VTE event or while on anticoagulation
- Tx: Pts w/ protein C deficiency are classically at risk for warfarin-induced skin necrosis and should be bridged w/ LMWH.

Antithrombin III deficiency

- Epidemiology: Can be hereditary (gene mutation) or acquired (liver disease, warfarin therapy, protein losses such as from nephrotic syndrome, ECMO, hemodialysis, acute thrombosis, or disseminated intravascular coagulation).
- Pathophys: Inhibits thrombin (Factor IIa), Factor Xa, and Factor IXa. Heparin works by binding antithrombin III, so it is not an effective anticoagulant in patients with ATIII deficiency.
- Testing: ATIII functional assay assessing Xa inhibition
  - ↓ by acute thrombosis, UFH/LMWH, liver dz, nephrotic
  - ↑ by DOACs, direct thrombin inhibitors
- OR of VTE is 16. Anticoagulation as well as antithrombin III replacement are used for acute VTE and may also be used in prevention of VTE during surgery and pregnancy.

Antiphospholipid (Antibody) Syndrome

- Epidemiology: Acquired autoimmune multisystem disorder. Can be classified into thrombotic APS, obstetric APS, and catastrophic APS
- Pathophys: Antiphospholipid antibodies (aPL) are directed against phospholipid-binding proteins, which includes anticardiolipin, anti-beta2-glycoprotein, and lupus anticoagulant (a misnomer) (**Clin Exp Med 2017;17:257**)
- Dx (Sapporo APL Classification Criteria; **J Autoimmun 2014;48**):
  - At least one clinical criteria:
    - Vascular thrombosis (does not include superficial venous thrombosis)
    - Pregnancy morbidity: 1+ unexplained deaths of normal fetus at ≥10 weeks gestation, or 1+ premature births of normal neonate < 34 weeks gestation because of eclampsia/preeclampsia/placental insufficiency, or 3+ consecutive spontaneous pregnancy losses at <10 weeks gestation, unexplained by chromosomal abnormalities or by maternal anatomic or hormonal causes
  - Laboratory criteria (at least one of the following on two or more occasions, 12 weeks apart)
    - Anticardiolipin IgG or IgM (>40 GPL or MPL or above 99% percentile)
    - Anti-beta2-glycoprotein IgG or IgM (same threshold as above)
    - Lupus anticoagulant activity
  - Criteria made for research purposes. Clinical judgement required. Can diagnosed with negative/borderline testing if clinical picture consistent
- Pitfalls in interpreting assays:
  - LA unreliable on AC (false +) and acute thrombosis (false -); anti-CL and -GP not affected
  - ⊕ aPL Ab can be seen in infection, rheum dz, malignancy, meds w/o clinical APS
- Tx: For acute VTE, anticoagulate with LMWH bridging to warfarin rather than DOAC
  - Several trials have demonstrated that DOACs are less effective than warfarin in reducing VTE recurrence (**Blood 2018;132:1365**)
  - In pregnant patients, use LMWH due to warfarin's risk of teratogenicity
- Many other non-diagnostic criteria clinical features including stroke/TIA, thrombocytopenia, AIHA, pulmonary hypertension, ARDS, cardiac valvular thickening and nodules (Libman-Sacks endocarditis), CAD, cutenaous findings, acute/chronic renal failure, GI ischemia, etc.

Catastrophic Antiphospholipid Syndrome (CAPS)

- Classification criteria:
  - Evidence of involvement of 3+ organs, systems, and/or tissues
  - Development of manifestations simultaneously or in less than a week
  - Confirmation by histopathology of small vessel occlusion
  - Lab confirmation of antiphospholipid antibodies
- Definite CAPS: all 4 criteria. Probable can be considered based on looser criteria (not listed here)
- Frequently fatal; mortality rate approaching 50 percent
- Tx:
  - Treat identifiable precipitating infections
  - Anticoagulate with heparin in acute setting. When stable, transition to warfarin
  - High-dose systemic glucocortiocoids
  - Consider plasma exchange and/or IVIG, rituximab, and anti-C5 directed therapy

Disseminated Intravascular Coagulation

- Catchall term describing multiple possible disorders of hemostasis, processes where coagulation and fibrinolysis become abnormally dysregulated, leading to ongoing coagulation and fibrinolysis (**Thromb J 2016;14**)
- If there is a suspicion, consult hematology. Additional ddx to consider includes: massive blood loss, TTP, HUS, HIT, VKA, cirrhosis
- Central tenants of DIC are
  - It is unregulated and is a self-propagating feedback loop
  - It is diffuse, across entire circulation. Often involves multiple organ systems and when clinically apparent, it can rapidly lead to mortality
  - Usually a secondary marker of severe illness rather than its cause
- Dx: ISTH DIC or JAAM scoring system. DIC is divided into several types, based on degree of fibrinolysis:
  - Suppressed-Fibrinolytic Type**:** *Hypercoagulation* predominant with ↓ fibrinolysis.
    - Seen in *SEPSIS* (classic case in *Neisseria* infxn → protein C deficiency), late trauma, pancreatic cancer, adenocarcinoma
    - Microthrombi → organ failure. *RARELY* are bleeding symptoms present.
    - Labs: D-dimer ↑, PT/PTT↑, ATIII/Protein C/Protein S↓
    - Tx: *Treat underlying cause***.** Consider *HEPARIN (bolus and gtt)* if evidence of purpura fulminans – often large amounts needed (follow anti-Xa levels). Upfront factor concentrate. FFP per protocol with heme
  - Enhanced-Fibrinolytic Type**:** *Bleeding* predominant
    - Seen in APML, aortic aneurysm, metastatic prostate cancer, pregnancy (due to release of tPA from placenta), early trauma, aortic aneurysms
    - Due to activation of fibrinolysis → clots dissolving easily.
    - Labs: D-dimer ↑, PT/PTT can be WNL/↑, fibrinogen WNL
  - Balanced-Fibrinolytic Type**:** Balance achieved between bleeding/clotting
    - Often asymptomatic with lab abnormalities, but *may progress rapidly and imbalance.* Seen in solid cancers (prostate, vascular malignancies).

Hypercoagulability in Cancer

See Inpatient Cancer Complications: Anticoagulation and VTE for full discussion

Blood Products in Transfusion Medicine:

Type	Description	Indications	Notes
pRBC	1U = 330cc = $895 Processing 1. Leukocyte Reduction 2. Irradiation 3. Washed	- Goal Hb >7 (TRICC, TRISS and Villanueva trials) - Goal Hb >8 in HD instability, CAD/ACS, orthopedic/cardiac surgery - Autoimmune hemolytic anemia and myelodysplastic dz (no specific Hgb threshold) - Sickle cell dz (Hgb drop > 2 from steady state) - Most cancer pts tolerate Hb > 7 mg/dL and alternative thresholds have limited evidence base (**Cochrane 2012;2:CD009007**) - Thalassemia (pre-transfusion goal 9.5-10.5); aim for suppression of reticulocytes	- Assess response: 1U ↑ Hgb ~1 - pRBC is not a colloid solution (Hct ~55%) & will not exert same effect as hyper-oncotic colloid (25% albumin)
Platelets	1U = 6-pk = 300cc = $3400 Types 1. Apheresis platelets derived from 1 donor 2. Pooled platelets derive from multiple donors Processing 1. Leukocyte reduction 2. Irradiation 3. Washing	- Consider for low platelets *or* functionally abnl platelets: <10,000 → ppx against spontaneous bleeding, even in oncology pts (**Lancet 2012;380:1309**). Also consider antifibrinolytics in chronic or refractory thrombocytopenia i/s/o malignancy (**J Clin Oncol 2018;36:283**) <50,000 → major bleed, intra- or post-op surgical bleed, ppx prior to invasive operative procedures (limited evidence) <100,000 → post-cardiopulmonary bypass bleed, intracranial/ophthalmic surgeries (limited evidence) ITP → life-threatening CNS/GI/GU bleed, fatal hemorrhage is often preceded by wet purpura (mucus membrane bleeding). Otherwise, not beneficial Relative C/I: HIT, TTP → avoid PLTs unless bleeding, do not use as ppx	- Assess response at 30-60m after transfusion: 1U ↑ PLT ~ 30K. - Consider whether patient is hypo-proliferative versus high turnover when applying platelet thresholds - Limited evidence that apheresis platelets > whole blood derived platelets - Limited evidence that platelets reverse anti-platelet agents (PATCH) - To dx refractoriness, assess plt recovery (15-60m after) and survival (18-24h after); consult Blood Transfusion for platelet refractory workup (**NEJM 1997;337**)
FFP	1U = 250cc = $460 1 Dose ~ 10-20 cc/kg Noncellular portion of blood that is separated and frozen after collection. Contains all coagulation factors w/ max correction INR 1.7	- Active bleeding d/t a deficiency of multiple coagulation factors *or* isolated coagulation factors for which concentrate is not available - Cirrhosis: Coagulopathy is dominated by hyperfibrinolysis → Consider anti-fibrinolytics instead. Treating INR w/ FFP will likely ↑ bleeding d/t ↑ portal pressures. Routine pre-procedural ppx is *not* recommended (**Eur J Haematol 2020;104:15**) - ALF: Consider for thrombocytopenia and/or prolonged PT only if hemorrhaging or pre-procedurally - VKA reversal: IV Vitamin K first. Can also consider prothrombin complex conc. if concern for volume - DIC in presence of bleeding - Trauma, C*ongenital* TTP	- Effect < 6H d/t short $t_{1/2}$ FVII - Assess response immediately after transfusion: 1U ↑ coagulation activity ~ 10%
Cryo-Precip-itate	10U = 150 cc's = $2850 Contains factor VIII, factor XIII, VWF, and fibrinogen	- If fibrinogen 50–100mg/dL → 10 units - If fibrinogen 0–50mg/dL → 20 units - Advanced liver dz (w/ anti-fibrin.) - Massive transfusion w/ low fibrinogen *or* abnl ROTEM / TEG - Complex cardiac surgery - Obstetrical hemorrhage (**Trials 2012;17:13**) - F.VIII deficiency, VWD, uremia	- Fibrinogen replacement: 0.2 bag/kg provides 100 mg/dL fibrinogen, $t_{1/2}$ 3–5d - F.VIII or vWF replacement: cryo is last resort therapy

Coagul-ation factors	Types Single: VIII, VIII + vWF, IX, rF VIIa, ATIII 3-factor II, IX, X 4-factor II, VII, IX, X FEIBA	- Hemophilia - VKA reversal: IV Vitamin K and PCC	- Requires approval from Blood Transfusion Services - S/E: Allergic reactions, thrombotic toxicities
Anti-fibrin-olytics	Contains Lysine derivatives that bind to plasminogen to ↓ fibrinolysis and ↑ hemostasis Types (topical, PO, IV) 1. Aminocaproic acid (Amicar) 2. Tranexamic acid (TXA)	- Coagulopathy of trauma (CRASH-II trial) - Obstetric bleeding (WOMAN trial) - Cardiac surgery (ATACAS trial), ECMO - Advanced liver dz including liver transplantation, but ↑ thrombosis w/ variceal bleeding - Major orthopedic surgery - Platelet refractoriness d/t HLA alloimmunization - Fibrinolysis of serosal surface and closed space bleeding - Reversal of coagulation factor inhibitors	- Amicar: 4-5 g (1st hr) → 1g/h for 8h until bleeding controlled (Max 30 g/d) - TXA: 1 g over 10 min → 1 g q8h - S/E: Possible risk of seizures w/ TXA
Albumin	Types ~$40/bottle 1. 5% (iso-oncotic) 2. 25% (hyper-oncotic) Both contain 12.5g albumin & 154 mEq Na (isotonic)	- Cirrhosis + HRS: albumin 1g/kg/d x 2d (max 100 g/d), most RCTs include albumin 20–40 g/d after initial bolus - Cirrhosis + SBP: abx + albumin 1.5 g/kg @ D1 & 1 g/kg @ D3 (max 100 g/d) → -↓ HRS & mortality - Cirrhosis s/p LVP: 25% albumin (fixed 40g, NOT 1 bottle/L) after each LVP (4-6L) → -↓ AKI, hypoNa; NO mortality benefit - Shock: 5% albumin similar to 0.9% NS for IVF resuscitation (when albumin > 2) - ARDS: 25% albumin (fixed 25g) q8h x 3d + continuous lasix gtt x 3d → improved oxygenation, net-negative TBB (when albumin <2)	- C/I: traumatic brain injury (SAFE subgroup)
IVIG	Polyclonal IgG and trace plasma contaminants Types ($280/g)	-Hypogammaglobulinemia w IgG < 400: Administer 0.3 – 0.5 g/kg monthly -Immunosuppression in autoimmune dz	- S/E: Hemolysis in A recipients, aseptic meningitis, hyperosmolar renal tubular injury - Adjust dose for obese pt

Modifications to Blood Products and Indications:

Type	Preparation	Indications
Irradiated RBC	-Irradiated by gamma or X rays w/in 14 days of donation. -Shelf life 28 days from irradiation	-Pts w/ hematologic malignancy or pts undergoing lymphocyte depleting therapy -Reduces risk of transfusion associated GVHD (TA-GVHD), which result when donor lymphocytes attack host tissue, including bone marrow progenitors -Radiation inactivates donor lymphocytes
Washed RBC	-Remove plasma, platelets, and leukocytes → Re-suspend in an electrolyte solution. -Shelf life 24 hours.	-Patients w/ 1) hx of severe anaphylaxis or 2) hx of IgA deficient **and** hx of anaphylaxis
Leukocyte Reduced (LR)	-Remove 99% of all leukocytes occurs at collection. -Shelf life 42 days for RBC	-Reduces risk of febrile non-hemolytic reactions, CMV transmission and HLA alloimmunization in pts w/ repeated transfusions or heme malignancies. -Consider in transplant candidates for bone marrow, kidney, heart and lung (not liver)

CMV Reduced Risk	-RCT demonstrated equal risk reduction in preventing CMV infection w/ both LR and CMV sero-negative blood products	-Same indications above (leukocyte reduced)

Transfusion of Blood Products in ABO-incompatible hematopoietic stem cell transplantation patients (Transfus Med Hemother 2016;43:13 **,** Biol Blood Marrow Transplant 2013;19:1152
~ 50% of BMT patients have incompatible donor/recipient ABO. These patients receive more transfusions and are at risk for delayed cellular engraftment, red cell aplasia, and acute/delayed RBC hemolysis. Following HSCT, these patients may continue as "chimeras" w/ two distinct blood types.

1. Phase I Preparative regimen (induction): Transfuse recipient blood components
2. Phase II Engraftment: Transfuse donor and recipient compatible RBC, platelets and plasma, until ABO antibodies are undetectable. For example, in a Recipient O/Donor A, we can transfuse Type O pRBC and Type A platelets/plasma. Type O RBCs lack pathologic antigens that can be recognized by both Recipient O and Donor A. Type A platelets/plasma lack any dissolved antibodies which may target both Recipient O and Donor A
    a. Major ABO incompatibility: Recipient antibodies directed against donor RBCs result in hemolysis *at the time of infusion*. The reaction is identical to a hemolytic transfusion reaction.
    b. Minor ABO incompatibility: Donor antibodies directed against recipient RBCs results in delayed hemolysis and may begin *w/in 7-10 days* after transplantation. The antibodies are formed by B lymphocytes that are contained w/in the progenitor cell graft and referred to as passenger lymphocyte syndrome
    c. Bidirectional incompatibility: Both Major and Minor
3. Phase III Post-engraftment: Transfuse donor blood components

Transfusion reactions:

	Acute	**Delayed**
Immune mediated	AHTR, FNHTR, urticaria/hives, anaphylactic TRALI	DHTR, TA-GVHD, post-tx purpura
Non-immune mediated	Cold toxicity, citrate toxicity, sepsis, TACO	Iron overload, viral infx

Maintain low threshold to call the blood bank for workup of blood transfusion reactions. Stop transfusion immediately, maintain ABCs, check vitals frequently.

Acute hemolytic reactions
Incidence: occur w/in the first 15 minutes and can present w/ fevers, chills, rigors, back/flank pain, and e/o DIC or bleeding. Incidence 1 in 70-130K. ABO/Kidd incompatibility (pre-formed Abs) lead to intravascular hemolysis, and cytokine/complement activation. Rh/Kell/Duffy incompatibility cause less severe extravascular hemolysis.
Dx: Obtain UA, CBC w/ diff, LFTs, DAT, special slide
Tx: NS +/- Lasix for goal UOP >100cc/hr. Monitor for hypotension, AKI, DIC.

Febrile non-hemolytic reactions
Incidence: w/in 1-6 hours of transfusions, w/ low-grade fevers, chills, headache, flushing. Incidence 1 in 200-2500 (pRBC); 1 in 50-1600 (PLTs). Pathophysiology explained by donor WBCs which produce cytokines including TNF-alpha, IL-1, IL-6.
Dx: hemolytic workup negative
Tx: Tylenol, meperidine
PPX: leukoreduction (little evidence for pre-medication, institution dependent)

Bacterial contamination
Incidence: onset 15-60 minutes; typically includes rigors, fever, and if severe can cause septic shock.
Dx: gram stain, culture of both patient and transfused blood
Tx: antibiotics, quarantine of similar products

Urticaria
Incidence: can occur during or after transfusion. Caused by IgE-mediated hypersensitivity to donor plasma proteins.
Tx: pause the transfusion and treat w/ diphenhydramine. OK to resume transfusion w/ resolution of urticaria
PPX: washed products; some institutions will premedicate future transfusions

Anaphylaxis

Incidence: 1 in 20-50K. Occurs acutely in minutes, and can cause hypotension, angioedema, urticaria, wheezing, abdominal symptoms. Caused by IgE-mediated hypersensitivity, particularly in recipient lacking IgA or haptoglobin. Can also be seen w/ bradykinin-mediated flushing and hypotension in patients taking ACE-i or negative charged filters.
Dx: consider IgA deficiency
Tx: ABCs; supplemental O2 +/- pressors; intramuscular epinephrine Q15 minutes; methylprednisolone 125mg; diphenhydramine 25-50mg
PPX: washed products

Transfusion-related acute lung injury (TRALI)

Incidence: 1 in 5K (FFP > PLT > RBC); symptoms w/in 1-6 hours and can occur even shortly after completion of transfusion; characterized by hypoxemia (which can evolve into ARDS), +/- fever. Pre-transfusion stress activates lung endothelial cells and primes PMNs; donor anti-HLA antibodies attack primed recipient PMNs
Dx: normal BNP, CXR w/ findings consistent w/ ARDS
Tx: ABCs; O2; intubation
PPX: male donor plasma (fewer anti-HLA, anti-PMN antibodies); defer donors w/ prior associated TRALI cases

Transfusion-associated circulatory overload (TACO)

Incidence: 1 in 350-5K; symptom onset w/in 1-6 hours of transfusion start, characterized by cardiogenic pulmonary edema from volume overload. Highest risk in the elderly, pre-existing heart failure or kidney dz, and chronic anemias.
Dx: elevated BNP; CXR w/ pulmonary edema
Tx: O2, diuretics, +/- nitrates, NIPPV
PPX: slow transfusion rate

IVIG reactions

Incidence: 5-15% of infusions. Symptoms characterized by inflammatory symptoms such as fever, chills, flushing, myalgias, and can include anaphylactoid symptoms like urticaria, flushing, chest pain, N/V/, hypertension
Tx: stop IVIG; Tylenol, diphenhydramine, meperidine, +/- steroids
PPX: may need to reintroduce IVIG at slower rate and space out infusions

Delayed hemolytic reaction

Incidence: 1 in 2K; symptoms in days and characterized by fever, anemia, jaundice, flu-like syndrome. Caused by anamnestic IgG against previously exposed antigen (Kidd, Duffy, Kell) leading to extravascular hemolysis
Dx: DAT, DBili/LDH, spherocytes
Tx: none

Transfusion-associated graft versus host disease

Incidence: rare. W/in 2-30 days of transfusion, fever, rash, mucositis, diarrhea, hepatitis, pancytopenia. Caused by donor T cells attacking non-HLA matched recipient organs in the setting of immunosuppression or 1st degree relative donor.
PPX: irradiation

Post transfusion purpura

Incidence: more likely in women. Symptoms start 3-14 days after transfusion: purpura and mucocutaneous bleed. HPA-1A negative women develop anti-HPA-1A antibodies, which is common in donor platelets.
Dx: PLT <10K; anti-HPA-1A
Tx: IVIG or PLEX
PPX: HPA-1A negative platelets

Jehovah's witnesses:

Specific contraindications vary by individuals; if you anticipate a patient developing a transfusion requirement, go over specific blood products w/ them.

- Generally acceptable – hematinic (iron, folate, B12, recombinant human EPO); non-blood volume expanders (NS, LR), hemostatic agents (Amicar, TXA, DDAVP, albumin-free clotting factors)
- Sometimes acceptable – autotransfusion, HD/apheresis/CBP/ECMO, hemostatic products w/ blood fractions (coagulation factors, PCC), plasma-derived products (albumin, IVIg), products containing albumin (rhEPO, vaccines), BM/organ transplantation

- Generally unacceptable products – whole blood, pRBC, platelets, FFP, cryoprecipitate, autologous blood transfusion
- Bleeding/preoperative management – consider IV iron + rhEPO to speed up erythropoiesis; ensure folate/B12/iron are replete.
- Critically ill – consider rhEPO 200-300U/kg IV daily, or 250-500U/kg SQ QOD

Physiologic Changes in Pregnancy:

Mild anemia Hgb ≥10 ↑ plasma volume > ↑ erythropoiesis	Resolves by 6w postpartum
Mild thrombocytopenia Plt ≥100k ↑ plasma volume, placental sequestration	Resolves by 4w postpartum Drop to <150k likely to recur if happened before
Mild neutrophilia to WBC ≤20k	Resolves by 6d postpartum
Mild hypercoagulability risk of VTE ↑ 5X	Resolves by 8w postpartum Most blood-based diagnostics inaccurate

Pathologic Anemia in Pregnancy (Semin Hematol 2013;50:222):

- ↑ erythropoietic precursor demands during pregnancy:
  - iron deficiency common (treat even if not anemic)
  - folate deficiency possible if not supplemented
  - B12 deficiency possible esp. if prior bariatric surgery or Crohn's
- Hemoglibinopathy (thalassemia, sickle cell), RBC membrane dz (spherocytosis)
  - Women w/ sickle cell dz experience more complications in pregnancy, incl. infection, thrombotic events, eclampsia, spontaneous abortion. **Hydroxyurea contraindicated**. SCD complications treated with usual care.
- Consider AIHA, severe hypothyroidism, CKD

Thrombocytopenia <100k in Pregnancy (Semin Hematol 2013;50:222):

Cause	Other features	Tx
Preeclampsia/HELLP	HTN, proteinuria, MAHA, LFT abnl Occurs late in pregnancy	**Delivery**
ITP	Dx of exclusion Isolated thrombocytopenia	If Plts <30k, steroids ± IVIG starting 1w prior to delivery/procedure
AFLP	Presents like acute liver failure Occurs late in pregnancy	**Delivery**
DIC	MAHA, ↑PT/PTT, ↓fibrinogen Triggers: infection, placental abruption, retained fetus, amniotic fluid embolism	Supportive, address trigger
TTP	Neuro sx (FNDs, sz, stroke) MAHA, ADAMTS13 <10%	**PLEX** (or just plasma infusion if hereditary)
C-TMA	Severe AKI, MAHA Not improved by delivery	**Eculizumab**, often requires dialysis
APS	Hx fetal loss, thromboses lupus anticoagulant, anti-cardiolipin, anti-β2GP1	**Anticoagulate** (*no* warfarin; use **LMWH** or UFH). Treat as ITP if plts <30-50k
Other: SLE flare, drug-induced, sepsis, VWD Type IIb, HIT, MPN, hypersplenism, ST-HUS, ↓ B12/folate, liver dz, BM failure, viral (HCV, HIV, CMV, EBV)		

Transfusion thresholds: Major bleeding (50k), Vaginal delivery (30k), C-section (50k)
Avoid: Operative (foreceps, vacuum-assisted) vaginal delivery, fetal scalp electrode if maternal plts <80k, neuraxial analgesia if plts <80k

Bleeding Disorders in Pregnancy (Hem 2016;1:232):

- VWD: high postpartum and late (1 month) bleeding risk
  - Type 1 and Type 2: usually do not need ppx factor replacement
  - Type 3: factor replacement at time of delivery through 3-5d afterwards
  - FVIII levels in 3rd trimester predict bleeding risk (replace FVIII and VWF at delivery if <50 U/dL)
  - DDAVP use controversial
- Hemophilia: carrier or acquired
  - Measure factor levels and replace near delivery if low
  - Avoid operative (forceps or vacuum-assisted) vaginal delivery
  - Avoid fetal scalp electrodes unless have ruled-out fetal hemophilia

- Beware neuraxial anesthesia if factor levels low

Thrombosis and Thrombophilia in Pregnancy (**Blood Adv 2018;2:3317**, **Chest 2012;141:e691S**):

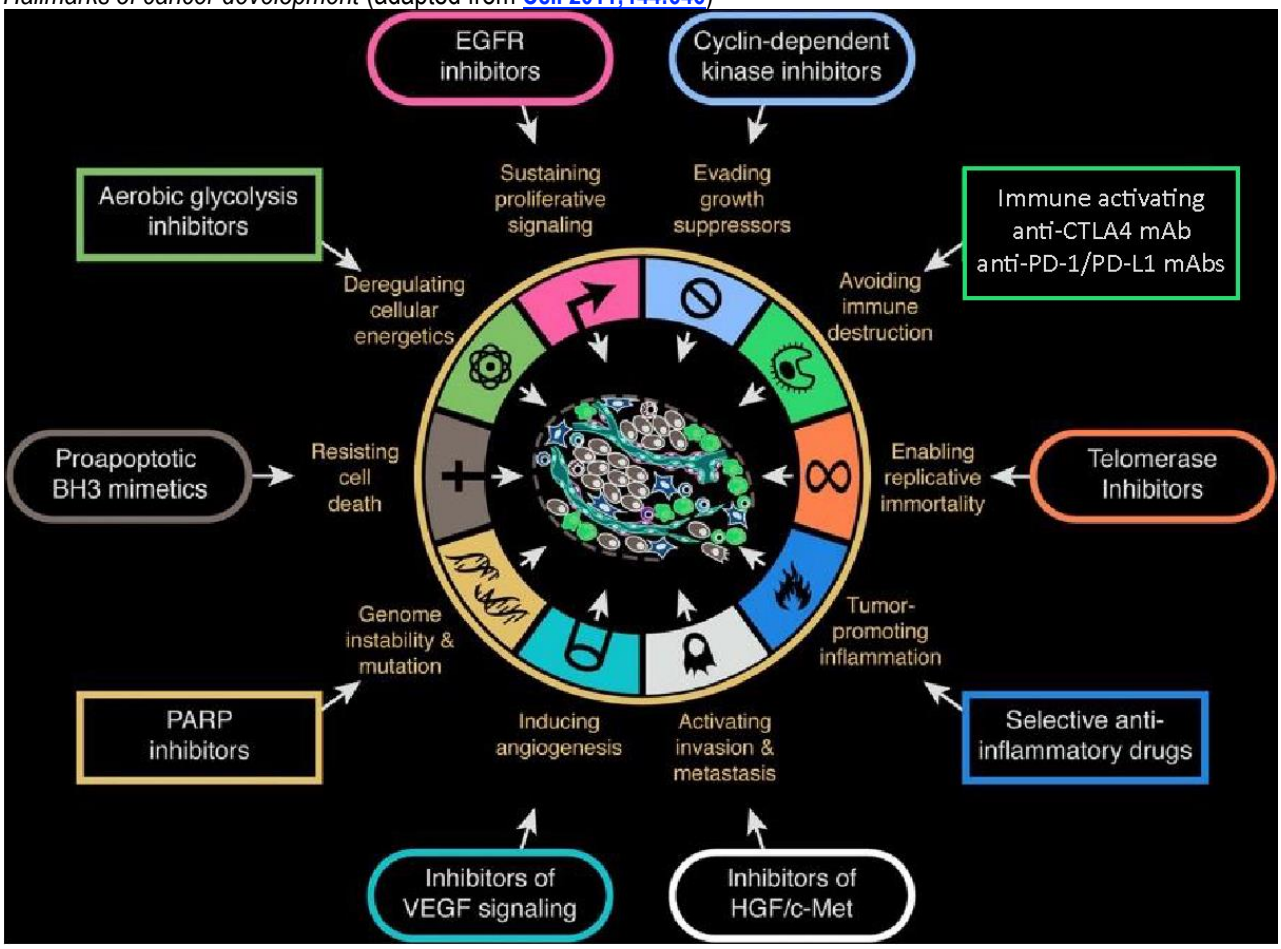
- Most DVT is L-sided due to compression of L iliac vein by gravid uterus
- VQ scan preferred to CT-PE
- AC choice:
  - **LMWH** is AC of choice in pregnancy. Change to **UFH at 36-37w** and then hold when labor begins
  - If HIT, use fondaparinux
  - Insufficient evidence for DOACs; if possible change to LMWH
  - **Warfarin is teratogenic** in the 1st trimester but has fetal risks throughout pregnancy. Share decision making on use: if low-risk mechanical valve or APS, suggest changing to LMWH for at least the first trimester
- For VTE continue therapy 6 weeks beyond pregnancy for at least 3 months total
- Antepartum/postpartum ppx AC reserved for those with history of VTE, homozygous FV Leiden, or PT 20210A.
- Postpartum ppx AC reserved for antithrombin, Protein C, Protein S deficiency (**Chest 2012;141:e691S**)

Brief Summary
Common cancer cell properties include the abilities to**:**

- **proliferate indefinitely** without reliance on normal growth-stimulating signals or check by growth suppressors,
- **maintain telomere length** to sustain this proliferative immortality,
- **metabolically adapt** and **form a blood supply** in order to generate energy and synthesize biomass to support cell division,
- **tolerate genetic instability** and circumvent death signals,
- **invade** and **metastasize**,
- **evade the immune system** (see section 3.3).

Cells must overcome multiple intrinsic and extrinsic barriers to become malignant and sustain primary and metastatic tumor growth. They must replicate indefinitely, compete for nutrients, spread through the body, and evade the immune system. In 2011, Weinberg and Hanahan expanded their original 2000 work to propose 10 hallmarks of cancer development (**Cell 2011;144:646**), which is a helpful framework to introduce cancer biology and the therapies developed from these understandings.

Hallmarks of cancer development (adapted from **Cell 2011;144:646**)



Sustaining proliferative signals
Proliferation is a defining characteristic of cancer and transformation involves the subversion of normally tightly regulated growth signaling pathways. Cancers may overexpress growth factors or their receptors (e.g. HER2 amplification in breast cancer), mutate or activate downstream signaling molecules (e.g. Raf activation in melanoma), and inactivate negative signaling molecules (e.g.

PTEN mutations in endometrial and CNS cancers, allowing increased PI3 kinase signaling), among many other mechanisms. Innumerable targeted therapies work by inhibiting these pathways.

Evading growth suppressors

The cell cycle presents an immediate barrier to unchecked cell division through a number of cell cycle checkpoints mediated by key regulators including Rb and p53. Cancers employ multiple mechanisms to bypass these checkpoints, including mutations of Rb and p53 or alterations in the expression or activity of other proteins within these regulatory pathways. As an example of a therapeutic strategy, the Rb pathway has been targeted in breast cancer via inhibition of Cyclin-dependent kinases (CDKs) with drugs like palbociclib (**NEJM 2018;379:1926**) and ribociclib (**NEJM 2020;382:514**). Intriguing preliminary data suggest CDK inhibitors may improve the efficacy of certain immunotherapies (**Nature 2017;548:471**).

Achieving replicative immortality

Even if cells are able to bypass cell cycle inhibitors to proliferate, they are limited by their telomeres. Telomeres are repetitive DNA sequences at the end of chromosomes that are required for chromosome stability and are shortened with each cell division. Cancer cell immortality requires mechanisms to maintain telomere length, with 80-90% of cancers achieving this through upregulation of telomerase, the enzyme that elongates telomeres, and the remaining fraction utilizing an alternative lengthening of telomeres (ALT) pathway. Targeting telomerase, such as with imetelstat, has shown some promise in myelofibrosis and certain myelodysplastic syndromes (**NEJM 2015; 373:908**).

Inducing angiogenesis

The growth of new blood vessels is tightly controlled by pro-angiogenic factors, like vascular endothelial growth factor (VEGF), and numerous anti-angiogenic factors. Rapid cell growth, as in tumors, exhausts available oxygen and nutrients. Resulting low oxygen tension stabilize hypoxia inducible factor (HIF) transcription factors that drive expression of VEGF-A, among other targets, to increase tumor vascularization. Inhibitors of VEGF and VEGF receptors (e.g. bevacizumab, aflibercept, ramucirumab, sunitinib, sorafenib, regorafenib, axitinib) have indications in a range of cancers from colorectal to lung (**Oncologist 2015;20:660**), but generally in combination with other forms of chemotherapy. Significant single agent efficacy has only been observed in clear cell renal cell carcinoma (RCC), which harbors constitutively activated HIF due to inactivating mutations of Von Hippel-Lindau (VHL), a critical component of the degradation pathway for HIF (sunitinib; **NEJM 2007;356:115**). Owing to the success of immune checkpoint inhibitors, combination therapy with a PD-1 inhibitor (axitinib and pembrolizumab) is now an additional frontline option (**NEJM 2019;380:1116**). A small molecule inhibitor of HIF-2α (PT2385) has also shown potential in phase I and II trials in RCC (**JCO 2018;36:867**).

Resisting cell death

Apoptosis, or programmed cell death, serves as a barrier to transformation by inducing cell death in response to physiologic stresses, including DNA damage. The frequent loss of the tumor suppressor protein p53 across many tumor types reflects a selective pressure to downregulate apoptosis-inducing signaling. Apoptosis is mediated by a cascade of signals resulting in caspase protease activation, and is generally regulated by the balance of pro- and anti-apoptotic members of the Bcl-2 family. Overexpression of Bcl-2, an anti-apoptotic factor, plays a role in chronic lymphoid leukemia and trials have demonstrated the efficacy of the pro-apoptotic family members, such as venetoclax (**NEJM 2019;330:2225**, **NEJM 2018;378:1107**). Interestingly, although the t(14;18) translocation that drives follicular lymphoma results in overexpression of Bcl-2, venetoclax has only modest single-agent efficacy in this disease and combinations are under active study.

Tolerating genome instability and mutations

A complex array of DNA-maintenance machinery exists in normal cells to identify and repair DNA damage and prevent mutations. Cancers, however, rely on mutations to evolve; therefore, DNA repair deficiencies can drive oncogenesis via increased mutation rates. For example, loss of the BRCA1 or BRCA2 DNA repair proteins predisposes to breast and ovarian cancers. However, it seems cancer cells have an optimum level of genomic instability, as demonstrated by the successful targeting of PARP DNA repair enzymes, such as olaparib, to generate cell-lethal levels of genetic instability in breast and ovarian cancers with BRCA or BRCA-like deficiencies in DNA repair (**NEJM 2017;377:523**, **NEJM 2019;381:2416**).

Deregulating cellular energetics

Cancer cells alter their metabolism relative to their normal tissue counterparts in order to provide the energy and macromolecular building blocks (proteins, lipids, nucleic acids, oligosaccharides) needed to support tumorigenesis. The metabolic programs adopted by cancer cells reflect the resources and limitations of their microenvironment (oxygen levels, substrate availability), and may, through their products (lactate or other immunosuppressive products), contribute to the microenvironment's immunosuppressive properties. A classic description of cancer metabolism is the so-called Warburg effect, first described by Otto

Warburg in the 1930s, in which cancer cells, even in the presence of oxygen, preferentially metabolize glucose to lactate (anaerobic metabolism or glycolysis) rather than employ the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (aerobic metabolism).This propensity for high glycolytic flux underlies the ability to image many tumors with labeled glucose in fluorodeoxyglucose (FDG) PET imaging. More recent work has built the theory that this peculiar use of "aerobic glycolysis" allows cancer cells to syphon off TCA cycle metabolites for macromolecule synthesis to support cell division, which in turn requires backfilling of the TCA cycle with carbon derived from glutamine and other substrates (**Cell 2017;168:657**).

These and other understandings have led to the hypotheses that various metabolic inhibitors might have therapeutic utility in cancer, including lactate dehydrogenase and glutaminase (e.g. CB-839) inhibitors, and these inhibitors have progressed to various stages of preclinical and clinical trial. Many oncogenes, including those encoding receptor tyrosine kinases, such as KRAS, MYC, and PI3K/mTOR signaling pathway components, and tumor suppressors, such as PTEN, LKB1/STK11, and VHL, regulate metabolism.

Underscoring the importance of metabolism in tumor biology, mutations in metabolic enzymes, including the TCA-cycle enzymes succinate dehydrogenase (SDH) and fumarate hydratase (FH), are the genetic underpinnings of several inherited cancer predisposition syndromes. One of the remarkable discoveries in the field of cancer metabolism in recent years was the identification that mutations in isocitrate dehydrogenase (IDH1 and IDH2) result in the formation of a so-called oncometabolite, or metabolic product that itself alters cell biology in ways that contribute to tumorigenesis. These mutations in IDH1 and IDH2 occur in several tumors and endow the mutant IDH enzymes the ability to convert alpha-ketoglutarate (α-KG) to (D)-2-hydroxyglutarate (D-2HG). Subsequent high levels of D-2HG result in inhibition of several α-KG-dependent enzymes, including those that regulate the methylation status of DNA and histones. Multiple IDH inhibitors are now approved for acute myeloid leukemia (AML) and are in clinical trial for gliomas. Lastly, it should be appreciated that many of the classic oncology drugs inhibit metabolic pathways. For example, methotrexate, pemetrexed, 5-fluorouracil, gemcitabine, cytarabine, and hydroxyurea, among others, either inhibit nucleotide synthesis directly or indirectly via inhibition of folate metabolism.

Activating invasion and metastasis

The vast majority of death related to cancer is due to metastatic disease. Metastasis requires cancer cells to invade local tissue, intravasate into blood or lymphatic vessels, disseminate through the body by way of these vessels, extravasate at distant locations, and then adapt to their new microenvironment and proliferate (**Cell 2017;168:670**). One critical mediator of these steps in carcinomas is thought to be activation of a mesenchymal transcriptional program, also termed the "epithelial to mesenchymal transition (EMT)." This is a developmental program normally active in migratory cell types in embryogenesis and wound healing. This transition permits cancer cells to shed cell-cell and cell-matrix adhesions and gain invasive and migratory qualities (**Nat Rev Cancer 2002;2:442**). Unfortunately, there are no treatments that directly target the mechanisms that underlie metastasis. To effectively block metastases, such treatments would need to be given as preventative therapy, further raising the efficacy/safety bar for this class of potential therapeutics.

Evading the immune system: See section 3.3

Molecular Diagnostic Techniques to Evaluate Tumor and Therapy Response

An exciting and wide array of molecular diagnostic approaches are currently used in the clinical setting and are being developed in basic labs, often employing new computational and machine learning approaches to integrate data from serum (liquid biopsies) and tumor tissue itself (see **Sequencing** section). Below, we provide an overview of key approaches that are, and will become, standard in clinical practice over the next several years (**Front Mol Biosci 2018;5:76**).

Immunohistochemistry (IHC): Staining of tumor tissue for surface and intracellular proteins to help define and classify tumor phenotype and guide therapeutic approaches. *Example: analysis for PD-L1 expression on tumor cells for consideration of anti-PD-1 therapy.*

Cytogenetics: Study of chromosome number and structure in cells ("macroscopic" chromosome interrogation). Identifies chromosomal abberations (e.g. translocations, deletions, amplifications). *Example: Philadelphia chromosome – translocation of chromosomes 9 and 22.*

- Testing for chromosomal abnormalities includes evaluation for aneuploidy (additions or deletions of chromosomes), translocations (reciprocal or unbalanced), subchromosomal amplifications and deletions.
  - Normal cells contain 46 chromosomes: 22 pairs plus XX or XY. Cancer cells often have gross alterations at the level of chromosomes.
- Major techniques include-
  - *Karyotyping:* Chromosomes are condensed during metaphase, stained with dye, and examined under a microscope for unique banding patterns. This technique can pick up differences in chromosome size and number as well as heterogeneity in centromere and satellite positions.
  - *Fluorescent in Situ Hybridization (FISH) (see below):* fluorescent probes are used to detect the presence or absence of specific sequences of DNA. Complementary DNA probes are generated to a sequence of interest and are hybridized with the sample. This technique can pick up gene copy number changes such as amplifications, deletions, translocations.
  - *Comparative Genomic Hybridization (CHG):* a molecular cytogenetic method for analysing copy number variations relative to ploidy (number of sets of chromosomes in a cell) level in the DNA of a test sample compared to a reference sample.

Examples of FISH Analysis in Oncology

Cancer	Target	Molecular Abnormality
MDS	5q	5q deletion
CML	BCR/ABL	t(9;22) translocation
AML	PML/RARA	t(15;17) translocation
Breast Cancer	HER2/neu	Amplification
Lung Cancer	ALK	Rearrangement

Flow Cytometry: Analysis of cell populations by cell number, size, shape, viability, and cell-surface markers. Also enables cell-sorting and single cell-isolation.

- Mostly used for hematologic cancers (leukemias and lymphomas) to identify heterogeneous populations of immune cells. Example: immunophenotyping for non-Hodgkin lymphomas (B vs T cell).
- Samples may be collected from bone marrow, lymph nodes, blood, or CSF.
- Cells are labeled with fluorescently conjugated antibodies against cell surface markers (to look for intracellular markers, cells must be fixed and permeabilized).
- Allows clinicans to evaluate proportions of lymphoid (B vs T cell), myeloid, NK, plasmacytoid lineages based on cell-surface marker expression.
- Workflow at MGH-
  - Tissue specimen collection.
  - Place EPIC order for flow cytometry; specify the panel you are interested in (for example "Lymphoma"), which defines the set of surface markers to be tested.
  - Results will populate as a "Pathology" sample.

Sequencing: Sequencing techniques facilitate the identification of mutations and other genetic alterations within tumor cell DNA, circulating tumor DNA (ctDNA), or cell free DNA (cfDNA). Knowledge of genetic alterations residing in primary, circulating, or metastasic tumor cells may help facilitate therapy selection against patient-specific molecular profiles (**Nature 2009;458:719**).

Emerging clinical practice follows longitudinal ctDNA profiling to assess clonal evolution and molecular residual disease (MRD) in liquid and solid tumors.

- Genetic alterations in cancer include:
  - Single Nucleotide Variant (SNV): point mutation (often causes missense or nonsense mutation) that may be rare or common in a population. May be referred to as single nucleotide polymorphism (SNP) if present in at least 1% of the population.
  - Insertion and deletion (Indel): Small duplications or deletions of consecutive nucleotides, can be "in-frame" (addition or subtraction of amino acids) or cause a frameshift mutation (e.g. premature truncation of protein).
  - Copy Number Variation (CNV): gene amplification or deletion.
  - Structural Variant (SV): genomic alterations that involve DNA segments larger than 1 kilobase (kb) resulting in possible gene fusions, translocations, or indels.
  - To learn more about cancer-specific mutations, go to **www.mycancergenome.org**
- Major techniques include:
  - Allele-specific qPCR: targeted detection of specific SNV, SV, or Indel.
  - Digital droplet PCR (ddPCR): higher sensitivity and specificity for detecting targeted mutations including SNVs, Indel, ctDNA
  - Next Generation Sequencing (NGS): allows *de novo* discovery of genetic alterations in patient's DNA sequence.
    - *Whole Exome Sequencing (WES):* sequencing of all known protein-coding genes.
    - *Whole Genome Sequencing (WGS):* sequencing of entire genome; both protein-coding (exon) and non-coding (intron) regions.
  - Tumor DNA sequencing: determine the nucleic acid sequence of a patient's tumor to identify mutations. This can be done by whole genome sequencing (WGS), whole exome sequencing (WES), or a targeted mutation panel
    - "SNAPSHOT Genotyping"- targeted NGS panel of known genetic mutations and alterations. *Example: BRAF V600E – A common SNV in melanoma.*
  - Circulating tumor DNA sequencing: determination of the nucleic acid sequence of circulating tumor DNA (ctDNA) or serum cell-free DNA (cfDNA) as a biomarker for tumor burden and mutation patterns.
    - "Gaurdant 360"- targeted mutation panel profiling of ctDNA captured in blood.
    - "Natera/Signatera"- WES of germline versus primary tumor DNA to identify putative clonal variants, followed by a tumor-informed PCR assay optimized to detect ctDNA with DNA variants. Typically used to assess and monitor for molecular residual disease (MRD) and recurrence.

- Workflow at MGH:
  - Tissue specimen collection (often via biopsy of solid tumor or blood from patient).
  - Pathologist confirms presence of tumor.
  - DNA extracted from formalin-fixed paraffin-embedded (FFPE) tissue samples.
  - NGS Snapshot performed in **MGH Center of Integrated Diagnostics**.
  - Snapshot Report can be viewed in the "Pathology" section of the Labs Tab in Epic.
  - Gaurdant 360 and Natera/Signatera reports can *sometimes* be found under media tab. You may need to ask primary oncologist for this information.
  - Some resources for understanding driver mutations compared to bystander mutations include: **http://www.cbioportal.org/** and **https://www.cancerhotspots.org/#/home**

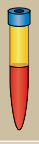
Other diagnostic approaches not currently in the clinic:

- Circulating biomarkers (cytokines, other proteins, exosomes, etc.)
- Epigenetic testing (serum and tumor DNA methylation analysis, other tumor epigenome sequencing such as CHIP-seq and ATAC-seq)
- Gene expression profiling of tumor tissue (RNA-sequencing, RNA FISH)
- Proteomic analysis of tumor tissue

Tissue sources:

- Solid biopsy (Primary tumor, metastasis or sentinel lymph nodes)
- Liquid biopsy (Serum ctDNA, cfDNA, protein, extracellular vesicles, RNA)

Features of solid biopsy samples that can be recapitulated in liquid biopsy samples (Nat Rev Genetics 2019;20:71)

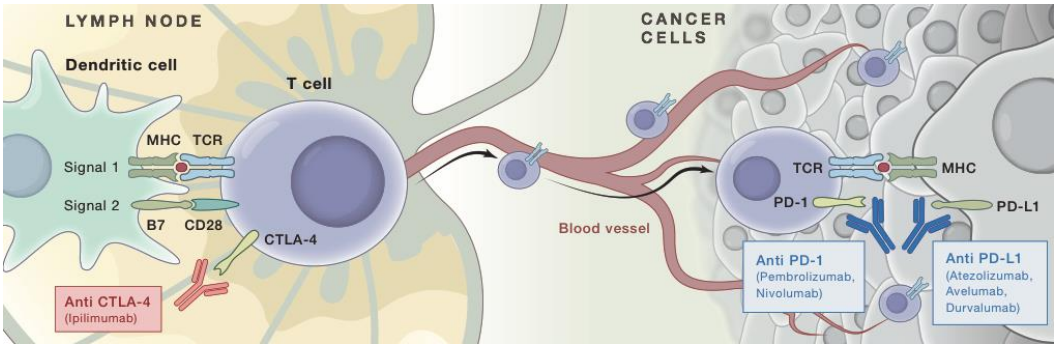
Features and parameters	Histopathology of solid biopsy sample	Analysis of ctDNA in liquid biopsy sample
		
Molecular marker		
Tumour burden	Tumour size informs about burden	ctDNA VAF informs about tumour burden
Subtype classification	Mostly based on histology but also on expression profiles	Might be based on tissue deconvolution and RNA and/or DNA markers
Tumour evolution	Hard to assess because longitudinal sampling is not feasible but can be deduced from intratumour heterogeneity	Phylogenetic ctDNA construction; longitudinal sampling easily achievable
Quality issues		
DNA quality	Mostly isolated from FFPE tissue and is prone to artefacts	Highly fragmented DNA, short half-life and low overall yield
Detection limit	Microdissection often needed; subclonal mutations often in a low range	Often low VAF in the range of background noise of analytical methods
Standardization	Some SOPs available	Lack of SOPs, but development in progress

ctDNA, circulating tumour DNA; FFPE, formalin-fixed paraffin-embedded; SOP, standard operating procedure; VAF, variant allele frequency.

Brief Summary
The immune system has the potential to recognize (**immunosurveillance**) and eliminate incipient tumors, but its ability to do so is hindered by the ongoing evolution of tumors to reduce their antigenicity (**immunoediting**) and dampen immune function. Tumors that become clinically relevant have achieved **immune escape** via one or more avenues. Many of the mechanisms of escape and therapeutic tactics to reverse them can be organized by hearkening back to the normal steps in cytolytic (CD8, aka killer or cytotoxic) T cell activation and regulation.

Immune evasion by tumor cells
Immunosurveillance refers to the process by which the immune system recognizes and confronts transformed cells as they arise. There are three possible outcomes to this interfacing of tumors with the immune system: **elimination, equilibrium, and escape**.

Cytotoxic T cell activation and regulation:



Cancer Cell 2017;31:848

Successful cancer **elimination** likely takes multiple routes involving both the innate and adaptive immune systems, but cytotoxic (CD8) T lymphocytes (CTLs) are key players. CTLs can recognize tumors because of neoepitopes ("non-self" antigens) derived from mutations acquired by the cancers. CTLs may also recognize improperly expressed antigens (e.g. overexpressed proteins or developmental or germline proteins) that are not tumor specific, although the ability to respond to these antigens is more limited due the immune system's properties of central and peripheral tolerance. When cancer cells die, these tumor antigens are engulfed by antigen presenting cells (APCs, including dendritic cells) that then present these peptide fragments to T cells on MHC molecules (MHC1 in the case of presentation to CD8 cells, MHC2 for CD4 helper T cells) as the so-called "signal 1" of T cell priming. In the right co-stimulatory ("signal 2") and cytokine milieu (e.g. T cell help), this successfully activates naïve CD8 T cells to become CTLs (effector cells) capable of recognizing these antigens on cancer cells and carrying out cancer cell lysis.

Equilibrium results when the immune system checks the tumor enough to control it, but does not manage to eliminate it. Equilibrium is not so much cancer dormancy, but rather a result of the ongoing evolution of tumors to attenuate their tumor antigenicity, a process termed immunoediting. **Escape** refers to tumors that have outmaneuvered the immune system and have acquired the ability to grow and progress without effective hinderance by the immune system. Tumor cells can achieve escape through several avenues, including suppression of immunogenic antigen expression (immunoediting, often via downregulation of either antigen or MHC expression), expression of immune checkpoint proteins (e.g. PD-L1), or recruitment of suppressive populations of immune cells, such as Tregs and suppressive myeloid cells.

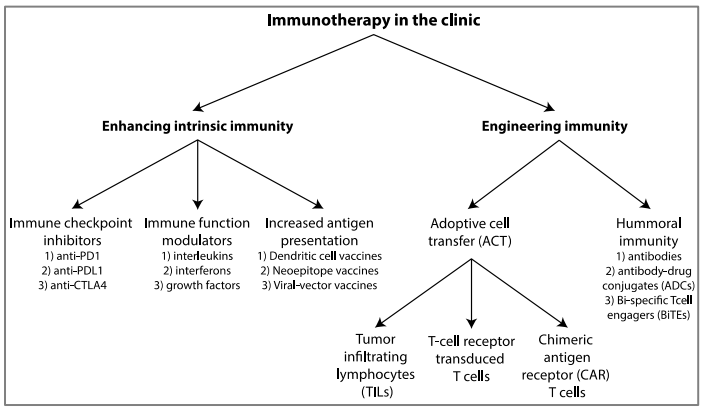
Immune cells in the tumor microenvironment
Cancer is a heterogeneous disease arising from a broad range of tissues and cell-types within the body. It has become increasingly clear the environment around cancer cells, termed the 'tumor microenvironment', can influence tumor evolution. A number of immune cell subtypes can be found within the solid tumor microenvironment, including cytotoxic T lymphocytes (CTLs), regulatory T cells (Tregs), B cells, natural killer (NK) cells, macrophages, and dendritic cells, among others. These cells may serve beneficial roles, such as direct cytotoxic killing of tumor cells, or may be harmful, such as by suppressing cytotoxic cells or creating an inflammatory milieu that promotes tumor evolution. In particular, the increased presence of effector memory CD4 and CD8 T cells, natural killer cells, and dendritic cells within several tumors is associated with longer patient survival; whereas, the presence of regulatory T cells and myeloid-derived suppressor cells is a negative prognostic indicator (**Genome Biol 2015;16:64**). Below we describe what is known about major immune cell subtypes in the tumor microenvironment (see **Immunity 2020;52:55** for further reading).

Cytotoxic T-cells (CTLs)
Several studies have demonstrated that early cancerous cells are visible to the immune system. CD8 expressing CTLs represent the major anti-cancer immune effector cells. The positive correlation between clinical outcome with checkpoint blockade therapy and neoantigen burden (**Science 2015;350:207**) suggests that CTL recognition of tumor-specific peptides predominantly underlies effective CTL anti-tumor immunity. There are two major ways these cells are generated: 1) the priming of naïve CD8 T cells in circulation after encountering tumor-specific peptides presented by dendritic cells on MHC1, and 2) reprogramming of tissue-resident or circulating memory T cells that have tumor specificity. Effective CD8 CTL tumor cell killing additionally requires proper trafficking of CTLs to the tumor microenvironment and creation of memory populations that enable immunity on re-exposure to tumor antigens.

Regulatory T-cells (Tregs)
The role of Tregs in the tumor microenvironment is less well understood. It is clear that Tregs are recruited to tumors and play a suppressive role in tumor immunity. Tregs require priming with tumor antigens in draining lymph nodes and exposure to antigen in the tumor microenvironment to exert their function. The key mechanisms of Treg suppression of tumor immunity are thought to be: 1) the expression of suppressive cytokines that inhibit CTL function, such as IL-10 and TGFb, and 2) impairment of dendritic cell function thus making them less effective in activating CTLs.

Myeloid cells
Macrophages and dendritic cells comprise the predominant myeloid cell types in the tumor microenvironment. The major function they serve in anti-tumor immunity is capturing and presenting antigens to T cells. This is especially the case for dendritic cells, and it usually occurs either within the tumor or in draining lymph nodes. Importantly, several myeloid cell functions may be co-opted by tumor cells to promote tumor evolution, including altering the balance between tissue repair (and antigen degradation) and effector functions that lead to an inflammatory environment (and antigen presentation). Myeloid cells known as myeloid-derived suppressive cells (MDSCs) suppress tumor immunity by expressing suppressive cytokines, including IL-10 and TGFb, and by recruiting Tregs, among other mechanisms.

Therapeutic approaches in immuno-oncology
Several strategies have been employed to boost the endogenous action of the immune system and to engineer the immune system to fight cancer. These approaches include checkpoint blockade, dendritic cell vaccines (**Science 2015;348:803**), neoantigen vaccines (**Nature 2017;547:217**), adoptive transfer of *ex vivo* expanded tumor infiltrating lymphocytes (TILs), and engineered T cells (**Cell 2017;168:724**), either with chimeric antigen receptors or cloned T cell receptors. Of these, only certain forms of checkpoint blockade and CAR T cells are FDA-approved for specific indications, and the remaining approaches are still considered experimental.



Steps in cytotoxic T cell activation and regulation, corresponding mechanisms of tumor subversion, and therapeutic strategies derived from these understandings

	Physiologic description	Mechanism of escape	Therapeutic tactic
Signal 1 (priming)	Activation of naïve CD8 T cells through TCR binding to antigen-loaded MHC1 on APCs. Often occurs in lymphoid tissue.	Immunoediting (downregulation of antigen expression)	CAR T cells (MHC-independent), oncolytic viruses to induce antigen expression by cancer cells, dendritic cell or peptide vaccines, T cells expressing engineered TCRs to known tumor antigens
Signal 2 (co-stimulation)	T cell CD28 binding to B7 (CD80/86) of APCs.		Antibody agonists in development (4-1BB, Ox40), second-generation CARs incorporating co-stimulatory domains

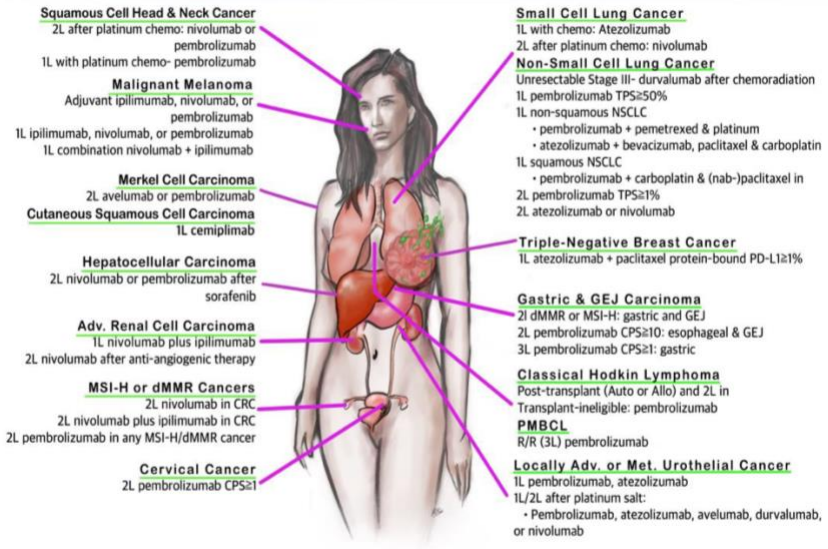
T cell help	CD4 cells secrete cytokines that influence CD8 T cell activation & differentiation into cytotoxic T cells		IL2, IL-15, armored CARs that express stimulatory cytokines
Target engagement and killing	Cytotoxic T cell TCR binding to antigen-loaded MHC1 on cancer cells.	MHC1 downregulation, immunoediting	CAR T and CAR-NK cells (MHC independent), BiTEs, oncolytic viruses (induce antigen expression), T cells expressing engineered TCRs to known tumor antigens
Checkpoints	Upregulated in response to T cell activation to reduce activity (internal brakes) (CTLA4, PD-1).	Tumor upregulation of PD-L1 (PD-1 ligand)	Checkpoint inhibitors (anti-CTLA1, anti-PD-L1, anti-PD-1), deletion of PD-1 from CARs
Suppressive cells	Tregs, MDSCs, M2 macrophages that suppress immune activation	Recruitment of these immunosuppressive cells to the tumor microenvironment through cytokines or chemokines	Preparative chemotherapy prior to cell therapy, radiation, ex-vivo expansion of TILs, armored CARs expressing stimulatory cytokines

TCR = T cell receptor, APC = antigen presenting cell, MHC1 = major histocompatibility complex 1 (expressed on all cells), CAR = chimeric antigen receptor (fusion protein that is essentially a portion of a immunoglobulin (i.e. to CD19, BCMA) on the cell surface and TCR signaling domains in the cytoplasm), NK cells = natural killer cells (do not require MHC engagement for cytotoxic activity), CAR-NK = NK cell engineered to express a CAR, TILs = tumor infiltrating (cytotoxic T) lymphocytes, BiTEs = Bispecific T cell engagers (antibodies that recognize both CD3 on T cells and a cancer cell target antigen to bring T cells and cancer cells into proximity), MDSCs = myeloid-derived suppressor cells.

Checkpoint blockade

The inhibition of immune checkpoint molecules to boost CTL function in the tumor microenvironment has led to a revolution in the treatment of many cancers. Anti-PD-1 (Pembrolizumab, Nivolumab) (NEJM 2012;366:2443, NEJM 2015;372:2018, NEJM 2015;373:1627, NEJM 2015;373:123), anti-PD-L1 (atezolizumab, avelumab, durvalumab) (NEJM 2012;366:2455), and anti-CTLA4 (ipilumumab) (NEJM 2015;373:23) antibodies have proven efficacious in, and been FDA approved for, the treatment of a variety of cancers (Figure 2), with a myriad of additional trials in progress. Additionally, the use of PD-L1 as a tumor marker to better guide usage is increasingly being used. In general, immune checkpoint blockade has proven most useful in tumors with high mutational burden, conceivably because neoantigen-recognizing CTLs exist and are poised to be disinhibited. Indeed, microsatellite instability-high (MSI-high) or mismatch repair-deficient tumors are a histology-independent indication for checkpoint blockade. However, checkpoint blockage can produce life-threatening autoimmunity, reflecting the role checkpoints play in homeostatic immune regulation. As the use of these treatments has become widespread, new mechanisms of tumor resistance have become apparent, such as mutations in the JAK-STAT and antigen presentation pathways (NEJM 2016;375:819, Cell 2017;168:707).

FDA approved indications for checkpoint inhibitors (from Cancers 2020;12:738):



Indications: 1L = first-line, 2L = second-line, 3L = third-line

T cell engineering

Two major approaches have been employed to engineer T cells to fight tumors:

1) adoptive cell therapy with CTLs expressing tumor antigen-specific T cell receptors (TCRs)
2) adoptive cell therapy with CTLs expressing chimeric antigen receptors (CARs)

Tumor antigen-specific T cell receptors (TCRs):

Next-generation sequencing technologies have enabled the identification and cloning of TCRs expressed on TILs. The production of CTLs that express these TCRs against tumor antigens has the advantage over CARs that intracellular antigens (displayed on surface MHC molecules) can be targeted. However, as engineered TCRs are cognate to a specific MHC-antigen complex, their generalizability as a therapeutic approach is limited by the diversity of MHC molecules in the human population. Trials with these engineered TCRs have had mixed results with perhaps CTLs expressing TCRs against NY-ESO-1/LAGE-1 antigen in sarcoma, melanoma, and multiple myeloma or WT-1 tumor antigen in AML among those showing the most promise to date (reviewed in **Cell 2020;181:46**). **KIMMTRAK (tebentafusp-tebn)** is the first TCR-engineered T cell therapy, which is FDA approved for uveal melanoma (**NEJM 2021;385:1196**).

CAR-T cells:

CAR-T cells offer a promising alternative adoptive cell therapy approach. CARs are synthetic constructs of single-chain variable fragments derived from monoclonal antibodies fused to signaling domains from TCRs. These constructs have the advantage that they do not require antigens presented on MHCs; however, they are limited to targeting cell surface proteins. Autologous T cells expressing CARs have shown remarkable efficacy in B cell and plasma cell malignancies refractory to other therapies (reviewed in **Cell 2020;181:46**). Approved CAR-T therapies target CD19 (on B cells) and BCMA (on mature B cells and plasma cells; **NEJM 2021;384**) (see table), but additional antigens are being explored. CARs for solid tumors are still in early development, and their efficacy has not been as dramatic to date. As with T cells expressing engineered TCRs, challenges faced by CAR T cell efforts include the identification of non-self tumor antigens to target (or ensuring of a therapeutic window when antigens are also expressed at low level on normal tissue), downregulation of the target antigen by tumors, and, in the case of solid tumors, hindered CAR trafficking to the tumor due to an unfavorable tumor microenvironment because of checkpoint ligand or inhibitory cytokine expression, population by suppressive cell-types (Tregs, MDSCs), or harsh metabolic conditions.

FDA-approved CAR-T therapies

FDA-appoved CAR-T cell therapy	Year	target	Approved original indication
Tisagenlecleucel (Kymriah)	2017	CD19	ALL
axicabtagene ciloleucel (Yescarta)	2017	CD19	Large B-cell lymphoma
Brexucabtagene (Tecartus)	2020	CD19	Mantle cell lymphoma
lisocabtagene maraleucel (Breyanzi)	2021	CD19	Large B-cell lymphoma
idecabtagene vicleucel (Abecma)	2021	BCMA	Multiple myeloma
Ciltacabtagene autoleucel (Carvykti)	2022	BCMA	Multiple myeloma

Acute Myeloid Leukemia (AML) and Acute Promyelocytic Leukemia (APL)

Epidemiology

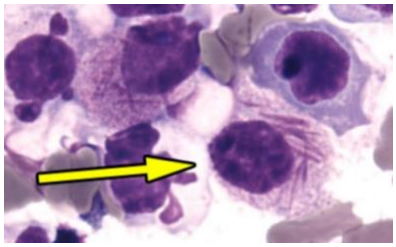
- Incidence: 3-5 cases per 100,000 persons overall, and 20 cases per 100,000 persons for age > 65, per year in the U.S. and Europe; the most common acute leukemia in adults (80% of cases).
- Median age of Dx: 65 y/o. (54% diagnosed at age > 65)
- Risk factors: Any that increase the risk of bone marrow damage, similar to those for MDS.
  - Advanced age (Core Binding Factor AML, i.e. CBF-AML, is an exception and occurs predominantly in younger patients)
  - Male gender (male:female ratio 5:3)
  - Exposures (e.g. benzene, tobacco, insecticides) and therapy-related from prior radiation (i.e. myeloablative) and leukemogenic chemotherapy (i.e. alkylating agents, topoisomerase inhibitors)—i.e. therapy-related AML, or **t-AML**
  - Survivors of childhood and young adulthood cancers (5-20% of patients w/ AML/MDS), highest risk for survivors of breast, gynecologic, and HL/NHL cancers
  - Preceding hematologic disorders (e.g. MDS, MPN, PNH)—i.e. secondary AML, or **s-AML**
  - Inherited genetic abnormalities (e.g. Down syndrome, Fanconi anemia, Bloom syndrome, familial *RUNX1, CEBPA, DDX41* mutations)

Natural history

- Clinical presentation: Symptoms of pancytopenia—anemia (fatigue, malaise), thrombocytopenia (gingival bleeding, ecchymoses, epistaxis, menorrhagia), neutropenia (infections). Bone pain seen less frequently (4%).
- Physical findings: Ecchymoses and petechiae (thrombocytopenia, DIC), violaceous nodules (leukemic cutis), gingival hypertrophy (leukemic infiltration), joint swelling (gout, leukemic infiltration). Palpable adenopathy and organomegaly are rare.
- Survival: Prognosis is poor. As much as 70% of pts > 65 y/o will die w/in 1y (**Appl Health Econ Health Policy 2013;11:275**, **Blood Cancer J 2016;6:e441**). Younger pts have higher remission rates and duration of remission.
- Causes of death: Hemorrhage, infection, DIC, leukostasis, TLS (see **ONC EMERGENCIES** chapter and **Complications** section below)

Complications

- Complications of AML arise from excess blasts and their tx. See **ONC EMERGENCIES** chapter for management and **Admission orders** below
- Leukostasis: Uncommon unless absolute peripheral blast count ≥50 x 10^9/L but can occur at any level. Myeloid cells are relatively large and do not deform easily → sludging (poor perfusion) → aggregate, forming thrombi (CNS, pulmonary, and coronary infarctions). Tx: high-dose hydroxyurea, leukapheresis (leukapheresis less commonly performed because often cannot keep up w/ proliferation and only transiently lowers counts).
- Fever: Should treat as neutropenic fever attributed to an infectious organism and **not d/t the leukemia itself** (see **ONC EMERGENCIES** chapter).
- DIC: If present w/ suspected Dx of new AML, strongly suspect acute promyelocytic leukemia (APL), although can be seen in other forms. May occur after starting chemotherapy.
- TLS: D/t rapid leukemia cell death; may be spontaneous or occur following tx, causing ↑Uric Acid, ↑K, ↑ Phos, ↓Ca^{2+}, ↓ renal function. Tx: Allopurinol, fluids, rasburicase if Uric Acid > 10, +/- phosphate binders.
- Acute promyelocytic leukemia (APL): **HIGHLY CURABLE AND ALMOST ALL DEATHS HAPPEN EARLY (e.g. w/in 1 week – 1 month) d/t DIC.** Thus, critical to suspect early and low threshold for empiric therapy. Once Dx suspected need to start all-trans retinoic acid (see **Tx for APL**) immediately. DIC or bleeding history typically present.
- Differentiation syndrome: Tx of APL w/ differentiation therapy (i.e. ATRA) can lead to cytokine release → edema, SIRS, hypoxemia, hypotension, serositis, renal failure Tx: steroids (discuss w/ attending). May see w/ some newer agents (e.g. IDH inhibitors).
- Myeloid sarcoma (chloroma): Extramedullary aggregates of leukemic cells, often soft tissues (gums), bone, lymph nodes, and skin (leukemic cutis). Tx: like AML, even if marrow w/o e/o leukemia.



Promyelocyte with Auer rods. (Source: HematologyOutlines)

Pathophysiology

- Hematopoietic progenitor cells undergo a stepwise accumulation of genetic mutations
- The transformed leukemic progenitor cells undergo clonal expansion and associated maturation arrest resulting in excess myeloid blasts
- There is failure of normal hematopoiesis in the bone marrow → cytopenias
- AML is a clonal disease that occurs from the development of recurrent somatic mutations in several pathways, which combine to result in an AML presentation. Not all cells in an AML patient will harbor the same mutations; the clonal architecture is an area of active investigation.
- Clinical assessment of recurrent mutations in AML is done via cytogenetic and molecular analysis.
  - Cytogenetics (Karyotype, FISH):
    - APL: t(15;17) producing PML-RARA
    - Core binding factor translocations (good prognosis): t(8;21) producing the fusion protein RUNX1-RUNX1T1. inv(16) or t(16;16) producing CBFB-MYH11
    - Others: deletions of chr 5, 7 (poor prognosis)
  - Molecular mutations are single-gene, somatic mutations (97% of AML patients). A large, whole genome sequencing project by The Cancer Genome Atlas (TCGA) group (**NEJM 2013;368:2059**) have identified 9 major categories of mutations based on function, including:
    - Transcription factor fusions: *PML-RARA*, *MYH11-CBFB*
    - *NPM1* mutations
    - Tumor suppressors: *TP53*, *WT1*, *PHF6*
    - DNA methylation: *DNMT3A*, *DNMT3B*, *DNMT1*, *TET1*, *TET2*, *IDH1*, *IDH2*
    - Activated signaling: *FLT3*, *KIT*, *KRAS/NRAS*
    - Myeloid transcription factors: *RUNX1*, *CEBPA*
    - Chromatin modifiers: *ASXL1*, *EZH2*, *MLL-X* fusions
    - Cohesin mutations
    - Splicesome mutations
- **For APL**: Myeloid differentiation is halted at the **promyelocyte** stage d/t the PML-RARA fusion protein

Molecular markers in AML have increasing clinical value (from NCCN 2021 guidelines):

Marker	Mechanism	Prevalence	Prognostic value
NPM1	Shuttle protein w/n nucleolus	28-35%	Isolated mutation → (+) prognostic Less (+) prognostic effect if co-occurring w/ FLT3 mutation
FLT3	Tyrosine kinase receptor; mutations either ITD (internal tandem duplication) or TKD (tyrosine kinase domain)	10-30% -ITD > KTD	**FLT3-ITD** → (-) prognostic effect, worse if biallelic **FLT3-TKD** → less clear, possibly (+)
CEBPA	Transcription factor in granulocyte differentiation	7-11%	Isolated BIALLELIC mutation → improved OS and remission duration Minimal effect if single mutation
IDH1/2	DNA methylation	6-12% -IDH2 > IDH1	**IDH1**: unclear, possibly (-) **IDH2**: unclear, possibly (+) IDH1/2 mutations mutually exclusive
DMT3A	DNA methylation	18-22%	Unclear effect, possibly (-) depending on age and co-mutations
KIT	Tyrosine kinase receptor	20% w/ CBF mutations	Unclear effect, possibly (-) depending on co-mutation or cytogenetic factors
KMT2A	Histone methyltransferase	2.8% in t-AML > *de novo* AML	Possibly (-) depending on fusion partner
RUNX1	Transcription factor	10%	(-) prognostic effect
ASXL	Transcription regulator	5-36%	(-) prognostic effect
TP53	Tumor suppressor	12-13%	(-) prognostic effect

Diagnosis

WHO classification system updated AML diagnostic criteria in 2016: certain cytogenetic findings are diagnostic of AML w/oout meeting >20% blasts and used for risk stratification.

Diagnostic tools for AML:

	Definition	Source of data
Phenotyping	Myeloid blast cells, as demonstrated by Auer rods, staining for myeloperoxidease (MPO), or expressing other myeloid markers	Immunohistochemistry, flow cytometry
% Blasts	> 20%	BM Bx
Cytogenetics	Genetic alterations at the chromosomal level, incl. loss or addition of a chromosome or part of a chromosome or a translocation among chromosomes	Karyotype and FISH
Molecular genetics	Somatic muations in single genes	SnapSHOT, NGS

For APL: Need expedited FISH looking for t(15;17), and/or expedited molecular testing for PML-RARA. Rapid turnaround critical; flow may be helpful but is not diagnostic.

Admission orders for leukemia:

- On Lunder, patients often present w/ new suspected AML. Admission work-up includes, diagnostic studies, evaluation of heart function (generally by echo) to evaluate patients prior to receiving cardiotoxic chemotherapy, and studies to monitor potential complications.
- **Use the Order Set "Leukemia Admissions", which includes relevant orders below:**
- General orders:
  - VS q4hr
  - Neutropenic precautions, neutropenic diet
  - Daily weights, Height x1 for BSA calculation (for chemo dosing)
- Labs:
  - CBC w/ diff, BMP, LFTs, Lipids, Type & Screen
  - TLS labs (q8hr): BMP, LDH, Uric acid, Ca, Mg, Phos
  - DIC labs (q8hr): PT/INR, PTT, D-dimer, Fibrinogen
  - Amylase, lipase (if required by protocol)
  - HBV and HCV serologies, CMV IgG (for BMT evaluation)
  - HLA typing (for BMT evaluation)
  - If a new patient has not had flow cytometry, flow should be sent in an expedited fashion
- Studies:
  - UA, CXR, EKG, TTE
- Prophylaxis
  - TLS: Allopurinol 300mg PO daily, IV fluids (typically NS @ 100-150cc/hr), rasburicase for extreme hyperuricemia > 10 (need attending approval)
  - Viral: Famvir 500mg PO daily (or acyclovir), entecavir if HBV-exposed
  - **No DVT prophylaxis** given pt's are often thrombocytopenic, at risk for DIC, or otherwise ambulatory
- **For APL:** Low threshold to suspect APL, particularly if DIC or bleeding is present. **Consult attending (fellow if overnight) ASAP for ATRA**
- For WBC >50k consult attending for hydroxyurea for cytoreduction
- Give blood products for Hct < 21, plt < 20, fibrinogen < 150 (cryoprecipitate)

Prognosis

- Risk stratification is crucial to reducing tx-related mortality and guiding decision to administer standard (intensive) induction vs lower intensity regimens, and to determine method of consolidation (i.e. transplant), and clinical trial enrollment
- Major prognostic factors include 1) cytogenetics, 2) somatic gene mutations, 3) performance status, 4) older age, and 5) secondary AML
  - Performance status: Karnofsky and ECOG performance scales are efforts to capture comorbidities that affect the mortality expected w/ tx. Karnofsky scores <60 and ECOG scores > 3 portend poorer outcomes.

- AML secondary to prior therapy or other hematologic disorders (i.e. t-AML, s-AML) have higher rates of drug resistance and poorer survival. Somatic mutations may identify s-AML features. CPX-351 (vyxeos) is a novel liposomal combination of daunorubicin and cytarabine at a fixed 1:5 molar ratio recently shown to have survival benefit in this patient population.

Molecular markers define Risk Status (from NCCN 2021 guidelines):

Risk Status	Genetic Abnormality	5-year survival
Favorable	- t(8;21): RUNX1-RUNX1T1 - Inv (16) or t(16;16): CBFB-MYH11 - Biallelic CEBPA mutation - NPM1 mutations w/o FLT3-ITD or w/ FLT3-ITD^{low*}	55-65%
Intermediate	- NPM1 mutation + FLT3-ITD^{high*} - NPM1^{WT} w/o FLT3-ITD or w/ FTL3-ITD^{low*} (w/o adverse-risk mutations) - t(9;11): MLLT3-KMT2A - Cytogenetics not (+) or (-)	24-41%
Poor	- t(6;9): DEK-NUP214 - KMT2A rearranged - t(9;22): BCR-ABL1 - inv(3) or t(3;3): GATA2,MECOM(EVI1) - -5 or del(5q), -7, -17/abn(17p) - Complex (> 3) anomalies - Monosomal karyotype - NPM1^{WT} and FLT3-ITD^{high*} - Mutations: TP53, RUNX1, ASXL1	5-14% *Lowest survival or poorest prognosis for monosomy

*low: low allelic ratio (<0.5); high: high allelic ratio (≥0.5). Allelic ratio (using DNA fragement analysis) determined as ratio of AUC "FLT3-ITD" and AUC "FLT3-wild type".

Tx for AML

- Standard intensive therapy involves 1) induction therapy to induce remission, and 2) consolidation (i.e. post-remission therapy) to eradicate residual disease and achieve lasting remission (Table 4-5).
- Typical Tx timeline:
  - if acute AML w/ WBC >50k, call attending ASAP whether to give hydroxurea for cytoreduction and prevention of TLS
  - **Induction** → **Day 14 BM Bx** to ensure no residual leukemia → **Reinduction** if residual leukemia detected → **Recovery BM Bx, once blood counts recovered,** to confirm remission (CR) → **Consolidation** when CR is achieved, or **Salvage** therapy for refractory disease
- Induction Tx considerations: Age, ECOG, co-morbid conditions, pre-existing MDS
  - For young patients or high relapse risk: aggressive induction chemotherapy (alone or as part of a clinical trial, w/ additional targeted agents)
  - For elderly or patients that are not fit for induction: venetoclax (BCL2 inhibitor) + hypomethylating agent (HMA) (5-azacitidine, decitabine), hypomethylating agent alone, or other less-intensive therapy, supportive care as well as strong consideration of clinical trials.
- Consolidation given after CR is achieved (generally 4-8 weeks from start of induction) can include 1) chemotherapy (commonly high dose Ara-C, aka HIDAC), and/or 2) allogeneic SCT, depending on age, performance status, and risk based on cytogenetics/mutations
  - Favorable: chemotherapy only
  - Intermediate: no consensus, but typically allogeneic SCT if able
  - Unfavorable: allogeneic SCT
- Why consider allo-SCT over chemotherapy:
  - Pros: Survival benefit in intermediate and poor-risk disease d/t graft-vs-leukemia effect, more recently an option for older pts w/ reduced-intensity conditioning
  - Cons: Transplant-related mortality (from GVHD and infection), suitable donor needed (less of an issue today w/ ↑ utilization of haplo-identical donors, ie. children, parents and siblings)

Intensive Tx approaches for AML based on risk:

	Favorable prognosis	Poor prognosis
Induction	"7+3"—7d cytarabine + 3d anthracycline +/- Gemtuzumab Vs clinical trial	"7+3"—7d cytarabine + 3d anthracycline + midostaurin if FLT3+ Vs clinical trial
Consolidation	"HiDAC"—high dose cytarabine or IDAC (Intermediate dose cytarabine if >60y) or clinical trial	Allo-HSCT vs. clinical trial. Patients not eligible for transplant may consider HIDAC or IDAC (Intermediate dose cytarabine if >60y).
CR rates	60-80%	40-55%
Tx related mortality	5-10%	20-30%
5-year disease-free survival	30%	5-10%

Adapted from Sekeres and Keng. Acute Myeloid Leukemia. Cleveland Clinic Center for Continuing Education 2014.

Novel AML agents:

Mutation	Agent	Indications
FLT3-ITD	Midostaurin (Rydapt)	ALL FLT3-mutated AML. Given after induction chemotherapy on day 8
	Sorafenib (Nexavar)	Relapsed/refractory (R/R) AML w/ FLT3 mutation (though not specific for FLT3 kinase)
	Gilteritinib	R/R AML w/ *FLT3* mutation
IDH2	Enasidenib (IDIFA)	R/R AML w/ *IDH2* mutation
IDH1	Ivosidenib (Tibsovo)	R/R AML w/ *IDH1* mutation
CD33+	Gemtuzumab (Mylotarg)	R/R AML or in less intense regimens, given w/ 7+3 for CBF AML

Tx for APL

- Low/Intermediate-risk (WBC ≤ 10k): **ATRA** (all-trans retinoic acid) **+ ATO** (arsenic trioxide). Both induce differentiation.
- Higher-risk (WBC > 10k): Evolving. Currently ATRA + anthracycline-based chemotherapy
- For unfit/older patients: **Venetoclax** (BCL2 inhibitor) + **hypomethylating agent (HMA)** (i.e. 5-azacitidine) shown to produce CR/CRi in 66% of patients w/ median overall survival 20.5 mo. Molecular predictors for response under investigation, but seems to include presence of *IDH1/2* mutations. TLS is rare w/ this regimen (unlike w/ venetoclax in CLL).
- **Differentiation syndrome in APL (25%):** life-threatening complication of ATRA and ATO where differentiated blasts can lead to cellular migration, tissue activation, and endothelial activation. (**NCCN Guidelines for AML v.2.2022**, **Ann Intern Med 1992;117:292**, **NEJM 2013;369:111**)
  - Unexplained fever, weight gain, respiratory distress, interstitial pulmonary infiltrates, and pleural or pericardial effusion w/ or w/o hyperleukocytosis
  - Ppx: If WBC >10,000 consider prednisone 0.5 mg/kg/day
  - Tx: **Dexamethasone 10 mg** IV q12h

Prophylaxis

- TLS: Allopurinol 300mg PO daily (may need to be renally dosed), IV fluids (typically NS @ 100-150cc/hr), rasburicase for extreme hyperuricemia (typically when uric acid > 10)
- Viral: Famvir 500mg PO daily (or acyclovir 400mg PO BID), entecavir if HBV-exposed
- Antifungal ppx : Low risk APL: no antifungal ppx. High risk APL: fluconazole 400mg PO daily (**Br J Haematol 2015;170:434**)
- No DVT ppx given patients are often thrombocytopenic, at risk for DIC, or otherwise ambulatory

APL/AML Pharmacology

Acute promyelocytic leukemia:

Agent	Mechanism	Dose	Side effects	Pearls
All-trans retinoic acid (ATRA) (Vesanoid)	Dissociates N-coR from PMA-RARA gene. Decreases proliferation and induces maturation and differentiation of APL cells leadings to apoptosis.	45 mg/m2/day split BID	Common: **peripheral edema, rash, ↑ LFTs** Warnings: pseudotumor cerebri, **differentiation syndrome** Long term: ↑ triglycerides and cholesterol	Hold for LFTs >5x ULN Order baseline triglycerides and cholesterol panel Pseudotumor cerebri: more common in younger pts (age <20)
Arsenic trioxide (Trisenox)	Induces morphological changes and DNA fragmentation leading to apoptosis of APL cells. Also causes degradation of the RARA oncoprotein.	0.15 mg/kg daily	Common: tachycardia, edema, hypotension Warnings: differentiation syndrome, hepatotoxicity, **QTc prolongation***	**Monitor QTc daily for first 3 days, if stable can monitor 2 days per week** **Hold for corrected QTc >500 msec** **Maintain K≥4 and Mg ≥2** **Caution w/ other QTc prolonging medications**

Per Lococo trial use Framingham formula to calculate corrected QTc (QTc=QT + 0.154[1000-RR]) (NEJM 2013;369:111)

Acute myeloid leukemia:

Agent	Mechanism	Dose	Side effects	Pearls
Idarubicin, daunorubicin	Inhibit topoisomerase II preventing relegation of DNA during DNA replication causing DNA strand breaks	Idarubicin 12 mg/m2 daily x3days Daunorubicin 60-90 mg/m2 daily x3 days	Myelosuppresion, mucositis, alopecia, N/V **Cardiotoxicity**	Maximum cumulative dose for anthracyclines Assess ejection fraction before administration, avoid in CHF Vesicant
Cytarabine	Structural analogue of pyrimidine nucleoside cytidine; Inhibits DNA synthesis by competitive inhibition of DNA Pol	100-200 mg/m2 continuously, days 1-7	**Myelosuppression**, N/V, flu-like syndrome, diarrhea, increase LFTs, **hand-foot rash**	
High dose cytarabine (HiDAC)	Above	Doses >1,000 mg/m2 Example: 3,000 mg/m2 q12h on days 1, 3, 5	Above toxicities plus: **Cerebellar toxicity** (old age and renal impairment=risk factors for cerebellar toxicity) **Conjunctivitis**	**Dexamethasone eye drops** until 72 hours after last dose to prevent conjunctivites Frequent cerebellar checks

Midostarin (Rydapt)	Inhibits FLT3 receptor signaling and cell proliferation, induces apoptosis in ITD- TKD-mutant expressing leukemia cells	50 mg PO BID days 8-21 of 7+3	QTc prolongation, rash, increase LFTs, arthralgia **Dose limiting toxicity: GI toxicity**	Administer antiemetics as premeds Administer w/ food for absorption Drug interaction: major CYP3A4 substrate, **caution w/ CYP3A4 inhibitors (posaconazole, voriconazole)**
Gemtuzumab Ozogamicin (Mylotarg)	CD-33 directed monoclonal antibody-drug conjugate. Binds to CD33, internalizes into leukemia cell, and binds to DNA → DNA strand breaks & apoptosis	Dosing depends on if w/ 7+3 versus single agent. Refer to lexicomp/package insert	Infusion related reactions, hemorrhage, rash, QTc prolongation **BBW: hepatox incl. veno-occlusive dz**	Premedications: acetaminophen, diphenhydramine, methylprednisolone Tx w/ gemtuzumab is risk factor for VOD if HSCT
Enasidenib (IDHIFA)	IDH2 inhibitor: Mutant IDH2 inhibition results in ↓ 2-hydroxyglutarate (2-HG) levels, ↓ abnl histone hypermethylation, and restored myeloid differentiation	100mg PO daily	N/V, diarrhea, elevated bilirubin*, hypophosphatemia, hypokalemia **<u>Warning:</u> Differentiation syndrome (median onset 48 days, as early as 10 days)**	Administer antiemetic as premed Treat differentiation syndrome w/ dexamethasone 10mg q12h
Ivosidenib (Tibsovo)	IDH1 inhibitor: see above	500mg PO daily	N/V, diarrhea, ↑ LFTs, arthralgia, fever, fatigue **<u>Warning:</u> QTc prolongation differentiation syndrome (median onset 29 days)**	Administer antiemetic as premed Drug interactions: dose reduction is necessary if administered w/ strong or moderate CYP3A4 inhibitors (posaconazole, voriconazole) Caution w/ other QTc prolonging medications
Venetoclax (Venclexta)	BH3-mimetic (BCL2 inhibitor): Promotes activ. BAX/BAK→ mito. outer membrane permeab., → apoptosis. w/ 5-azacitidine targets leukemic stem cells.	400 mg PO daily	Cytopenias, infections, nausea, vomiting, diarrhea, TLS (1%)	

Response in AML (from NCCN 2018 Guidelines):

Types	Definition
Complete Response (CR) Morphologic Cytogenetic Molecular	BM < 5% blasts, none w/ Auer rods ANC > 1,000 & Plt > 100k No extramedullary disease Transfusion independence Normal (if previously noted cytogenetic abnormalities) Negative (only relevant for APL and Ph+ but evolving for other mutations as well)
CRi	BM blasts < 5% ANC < 1000 **OR** Plt < 100k Transfusion independent but persistent cytopenia
Partial Remission	5-20% blasts on BM but at least 50% decrease from BL Normalized CBC (ANC > 1000, Plt > 100k)
Induction failure	Failure to attain CR following at least 2 courses of intensive induction therapy ("7+3" x 2 OR "7 + 3" → HIDAC)
Relapse following CR	Reappearance of blasts in peripheral blood BM blasts > 5% not caused by BM regeneration

Relapsed/Refractory AML

- Patients w/ relapsed/refractory disease have a poor prognosis w/ few available options. Tx is based on age at relapse and if early (<12 mo) or late (> 12 mo) since CR
- Therapy options include (a) clinical trials (b) chemotherapy (aggressive or less aggressive, +/- novel agents depending on cytogenetics/molecular markers) followed by HSCT if CR, (c) repeat initial induction therapy, or (d) best supportive care
- Aggressive chemotherapy regimens incl. purine analogs (fludarabine, clofarabine, etc.) demonstrate CR rates of 30-45%, w/ clofarabine > fludarabine
- For R/R AML s/p HSCT, can consider azacytidine, decitabine or clinical trial followed by donor lymphocyte infusions (ORR 30%) if in CR or second transplant if appropriate

Acute Lymphoblastic Leukemia (ALL)

Epidemiology

- Incidence: 1.6 cases per 100,000 persons per year in the US. Most common cancer in children and most common cause of death from cancer before age 20y
- Age: Peak 1-4y, median 15y, biphasic w/ incidence greatest age < 20y and > 60y
- Risk factors: Similar to AML (genetic and environmental factors)
  - Genetic syndromes: Down syndrome, neurofibromatosis type 1, Bloom syndrome, ataxia-telangiectasia, Fanconi anemia, Klinefelter syndrome
  - Inheritance of allelic variants: *ARD5B*, *IKZF1*, *CEBPE*, *CDKN2A*, involved in hematopoietic differentiation and proliferation.
    - Inheritance of one allele increases risk by 50%.
    - Inheritance of all four alleles increases risk by 10-fold (**Lancet 2013;381:1943**)
  - Exposures: radiation and chemicals; supporting data is poor
  - Infections: studies postulate that ALL may in part relate to a dysregulated immune response to common infections (**Lancet 2013;381:1943**)
- AYA population: less likely to have favorable genetics compared to children and more likely to have ALL w/ BCR-ABL (Ph+)

Natural History

- Clinical presentation: Signs of anemia (pallor, fatigue), thrombocytopenia (bruising, bleeding), and neutropenia (infection). B-symptoms (fever, NS, WL). May have bone pain.
- Physical findings: May see lymphadenopathy, hepatosplenomegaly, signs of ↑ ICP (CNS involvement), painless testicular enlargement (testicular involvement), palpable non-pruritic rash (leukemia cutis), mediastinal mass (especially T-cell ALL).
- Survival: Cure rates are ~90% for childhood ALL. Outcomes are much poorer in young adults (5-y survival 42 – 63%), adults (5-y survival 10-15%) and in infants (children < 12 mo) (**Lancet 2013;381:1943**).
- Causes of death: Hemorrhage, infection, leukostasis, TLS

Pathophysiology

- Leukemogenesis involves recurrent genetic alterations affecting the B-cell (80-85% of ALL) or T-cell lineage (15-20% of ALL). Self-renewal and normal B- or T-cell maturation are dysregulated.
- Mutations are 1) cytogenetic (e.g. translocations) or 2) molecular (single genes)
  - General ALL:
    - Cytogenetic: hyper/hypoploidy. Hypoploid clones all convey poor prognosis are categorized as near-haploidy (23-29 chromosomes), low hypoploidy (33-39 chromosomes), or high (42-45 chromosomes).
    - Molecular: *TP*53, *Ras*, *JAK-STAT* signaling
  - A/w B-cell ALL:
    - Cytogenetic and molecular:
    - Philadelphia chromosome positive ALL (Ph+): *BCR-ABL1*
    - Philadelphia chromosome-like (Ph-like): Highly diverse group of activating mutations in tyrosine kinase signaling, resulting in similar gene expression profile as Ph+ (**Blood 2017;129:572**).
    - Others: Various other translocations (*ETV6-RUNX1*, *TCF3-PBX1*, *MLL*-multiple partner genes) and mutations (*PAX5*, *IKZF1*, *EBF1*)
  - A/w T-cell ALL
    - Cytogenetic: Translocations involving *TAL1*, *TLX1*, *TLX3*, *LYL1* into the T-cell antigen receptor loci
    - Molecular: *INK4/ARF*, *WT1*, *PHF6*, *NOTCH1*

Diagnosis

- Classification is broadly divided into B-cell ALL and T-cell ALL
- 2008 WHO classification guidelines are based on 1) morphology, 2) immunophenotype, and 3) cytogenetics
  - Morphology (via BM bx): Mainly to distinguish ALL from AML and quantitate %blast
    - B-cell and T-cell ALL are virtually indistinguishable and may be hard to distinguish from AML (Auer rods are not present)
    - Cells in ALL are smaller than AML, more homogeneous in appearance, and lack granules, Auer rods, and prominent nucleoli, but **flow cytometry/IHC is required**
  - Immunophenotype (via flow cytometry or IHC stains): For Dx and subclassification of B- vs T-lineage ALL and distinguish from AML. Relevant classification includes early/precursor B-cell, mature B-cell, and mature T-cell
  - Cytogenetics (e.g. karyotyping, FISH): Karyotype changes are used to determine prognosis and therapy (see **Prognosis**)
- Patients need LP at Dx to assess CNS involvement regardless of symptoms

Characteristic Immunophenotypes:

B-cell ALL Type	Immunophenotype
Early pre-	**+TdT**, CD19/CD22/CD79a, **No CD10**
Pre-	**+Cytoplasmic Ig**, **CD10**/CD19/CD22/CD79a
Mature	**+Surface Ig**, +lambda/kappa LCs, **No TdT,** +/-CD20
T-cell ALL	Cytoplasmic **CD3** (blasts) or cell surface **CD3** (mature) Variable expression of CD1a/CD2/CD5/CD7, +/- CD52, +/- TdT

Common Molecular Abnormalities (Adapted from NCCN 2018 Guidelines):

Cytogenetics	Gene	Frequency	
		Adults	Children
Hyperdiploidy (> 50 Ch)		7%	25%
T(9;22) → Ph+	BCR-ABL1	25%	2-4%
T(12;21)	ETV6-RUNX1	2%	22%
"BCR-ABL1-like" → Ph-like	Various	10-30%	15%
T(11;14)	TCRs (α,δ)	20-25%	10-20%
T(8;14), (t2;8), t(8;22) "Burkitts"	c-MYC	4%	2%

Prognosis

- Clinically, **minimal residual disease (MRD)** is defined as ≥ 0.01% ALL cells, following tx used for prognostic evaluation. WBC and age at Dx are also prognostic in precursor B-cell ALL; they are less prognostic for T-cell ALL
- Early B-cell ALL (most common immunophenotype):
  - Favorable risk:
    - NCI standard risk group: WBC < 50k, age < 10ys
    - Cytogenetics: Trisomy 4 and 10, *ETV6-RUNX1* t(12;21), hyperploidy
    - Rapid response to tx: <0.01% minimal residual disease on Day 29 BM
  - Unfavorable risk:
    - NCI high risk group: WBC ≥ 50k, age ≥ 10ys
    - Cytogenetics: MLL rearrangements, iAMP21 amplification, Ph+, Ph-like, hypoploidy
    - Slow response to tx: ≥0.01% minimal residual disease on Day 29 BM
    - CNS or testicular disease
- Mature T-cell ALL: Generally considered high risk (d/t disease biology and also has less therapeutic options available). Tends to have elevated WBC and occurring in older patients
- Mature B-cell ALL: Poorer prognosis than precursor B-cell. Almost all cases are a/w t(8;14) translocation, which can also be seen in Burkitt lymphoma
- AYA patients (age 15 – 39): have better outcomes than older adults but worse outcomes than children. Prognosis is complicated by variation in protocols used, different response to tx, and differences in cytogenetics/molecular abnormalities in AYA v. pediatric populations
  - Patients age 15 – 21 had greater EFS when treated w/ pediatric regimen, which tend to have higher-intensity systemic and IT chemotherapy regimens
  - Patients older than 10 are more resistant to chemotherapy
  - AYA patients have lower frequency of favorable cytogenetic abnormalities (i.e. hyperdiploidy, ETV6-RUNX1), and their benefits may decline w/ age
  - AYA patients are far less likely to be enrolled in clinical trials (2% v. 60% in children)

Treatment

- Divided into 1) induction, 2) consolidation (can be multiple), 3) intensification (if needed), 4) CNS therapy (if needed), 5) maintenance, 6) transplant (especially if high risk). Sequence can vary w/ different protocol and include special considerations for AYA population.
- Common induction agents:
  - B-cell ALL:
    - *If BCR-ABL1 negative*: vincristine, asparaginase, daily steroids
      - Pediatric-inspired regimens often include significantly more steroids, as well as asparaginase
      - Hyper-CVAD is common regimen for adult ALL
      - Rituximab is added if CD20+
    - *If BCR-ABL1 positive*: TKI (e.g. dasatinib) are added to traditional induction chemotherapy
      - Recent trials suggest TKI combined w/ less-intensive chemotherapy or immunotherapy may be promising strategy moving forward (**NEJM 2020;383:1613**)
    - Pediatric-inspired regimens favored for AYA patients given superior outcomes in multiple trials
  - T-cell ALL: Often treated w/ similar regimens to B-ALL
- Consolidation agents (4-8 mo): cytarabine, methotrexate, anthracyclines (e.g. daunorubicin), alkylating agents (e.g. cyclophosphamide), etoposide
- Maintenance agents (30-40 mo): 6-MP (Purinethol), vincristine (Oncovin), methotrexate, prednisone (POMP regimen)
- CNS disease warrants intrathecal chemotherapy, such as high-dose methotrexate, as well as irradiation. Dasatinib is often used for Ph+ ALL because of ↑ CNS penetration.
- For refractory/relapsed B-ALL, FDA has recently approved:
  - Blinatumomab (Blincyto, for CD19+ disease)
  - Inotuzumab ozogamicin (for CD22+ disease)
  - Chimeric antigen receptor (CAR) T cell therapy (tisagenlecleucel [Kymriah]) for CD19+ disease
  - Nelarabine is used for R/R T-ALL
- For AYA patients important to consider pregnancy testing, fertility consultation, and means of fertility preservation
- Allo-HSCT is important consideration for high-risk patients, such as Ph+ ALL; however, studies are actively investigating how MRD-data can be used to make decisions regarding transplant.

Pediatric versus adult protocols (Curr Hematol Malig Rep 2014;9:158):

- Pediatric protocols: Higher doses of non-myelotoxic agents: vincristine, steroids, asparaginase. Late intensification: induction-like tx courses. Higher doses of MTX. Continuous exposure to chemotherapy. Delay in stem cell transplant (i.e. if relapsed disease).
- Adult protocols: Higher doses of anthracyclines, cytarabine, often include cyclophosphamide and etoposide. Prolonged neutropenia results in loss of continuous exposure to chemotherapy. Earlier stem cell transplant.
- Adolescent and young adult population: 15-39 yo. Benefit from pediatric-inspired protocols.

ALL Prophylaxis

- TLS prophylaxis: allopurinol and IVF
- PCP prophylaxis: 1 tablet Bactrim SS daily or atovaquone 1500 mg PO daily
- HSV prophylaxis: Famvir 500mg daily or acyclovir 400mg PO BID
- Antifungal prophylaxis: Fluconazole 400mg PO daily
- Stress ulcer prophylaxis (while on steroids): famotidine 20mg PO daily
  - Caution w/ PPi (omeprazole) while on methotrexate and dasatinib

ALL Pharmacology:

Agent	Mechanism	Dose	Side effects	Pearls
Vincristine	Binds to tubulin, inhibiting microtubulin formation. Causes cell cycle arrest during mitosis.	Usually 2 mg/dose given on multiple days (e.g. days 1, 8, 15, 22 during AYA induction)	Peripheral neuropathy, constipation, myelosuppression, SIADH	Bowel regimen to prevent constipation
Methotrexate	Inhibits conversion of folic acid → tetrahydrofolate by competitively inhibiting dihydrofolate reductase → inhibition of DNA synthesis via blockage of thymidylate and purine synthesis	Intermittently throughout phases (e.g. 40mg/m2 IV on day 3 during AYA induction)	Myelosuppression, nephrotoxicity, hepatoxicity, mucositis, pulmonary pneumonitis	Drug interactions: PPi, Bactrim
Doxorubicin	Inhibits topoisomerase II preventing relegation of DNA during DNA replication → causes DNA strand breaks	Intermittently throughout phases (e.g. 30 mg/m2 days 1-2 during AYA induction)	Myelosuppression, mucositis, alopecia, N/V Cardiotoxicity	Maximum cumulative dose for anthracyclines New HF - assess EF before administration, avoid in CHF Vesicant
Mercaptopurine	Purine antagonist that inhibits DNA synthesis	50 mg/m2 days 1-14 throughout consolidation, maintenance Dose titrated based on ANC	Myelosuppression, N/V, hepatotoxicity	Empty stomach Avoid w/ milk Pts w/ TPMT deficiency at risk of severe toxicity Drug interactions: allopurinol, tacrolimus
Pegasparaginase (Oncaspar)	Depletes serum of asparagine → deprives leukemia cells of exogenous source of asparagine. Normal cells	2,000 units/m2 (usually capped at 3,750 units) every 3-6 weeks	Hypersensitivity, bleeding and thrombosis, neuropathy, N/V, hypofibrinogenemia, pancreatitis,	Monitoring: amylase/lipase, triglycerides, fibrinogen, ATIII

	can resynthesize own asparagine, but lymphoblasts cannot and undergo apoptosis		hepatotoxicity, hyperglycemia,	
Blinatumomab (Blincyto)	Binds to CD19 on B-cells and CD3 on T-cells. Activates T cells by connecting CD3 in the T-cell receptor w/ CD19 on B-cells. Results in lysis of CD19+ cells.	4 weeks of continuous infusion then 2 week tx free interval x2 induction cycles Additional cycles have 8wk Tx free interval	Pancreatitis, hypersensitivity reaction, rash, neutropenia, thrombocytopenia **Warning: CRS, neurotoxicity**	Requires hospitalization for first 9 days of cycle 1 and first 2 days of cycle 2 Premedicated w/ dexamethasone
Inotuzumab ozogamicin (Besponsa)	CD-22 directed monoclonal antibody-drug conjugate. Binds to CD22, internalizes into leukemia cell, and binds to DNA resulting in DNA strand breaks and apoptosis	0.8 mg/m2 on day 1 and 0.5 mg/m2 on days 8 and 15 of a 21-day tx cycle	Myelosuppression, QTc prolongation, infusion reactions **Warning: hepatotoxicity, VOD**	Premedications: acetaminophen, diphenhydramine, methylprednisolone Tx w/ inotuzumab is a risk factor for VOD if going to HSCT

***Refer to CML section for tyrosine kinase inhibitors for Ph+ ALL**
***For information on CD19 CAR T cells, refer to CAR T cell section**

Response in ALL (from NCCN 2018 Guidelines):

Types	Definition
Complete Response (CR)	No circulating blasts or extramedullary disease, Trilineage hematopoiesis and < 5% blasts, ANC > 1000, No recurrence for 4 weeks
CRi	Above *except* platelet and/or ANC
Refractory	Failure to reach CR after induction
Progressive	Increase in blasts > 25%, New extramedullary disease
Relapsed	Blasts > 5% on BMBx or pB after CR
CNS remission	LP negative for lymphoblasts
Extramedullary remission	Head-to-toe PET/CT w/o disease

Chronic Myeloid Leukemia (CML)

- CML is a myeloprofilerative neoplasm (MPN) characterized by uncontrolled production of mature and maturing granulocytes, predominantly neutrophils
- **Epidemiology**:
  - 15-20% of leukemias in adults. 2-3 cases per 100,000 persons per yr worldwide. Median age at presentation is 64 y/o.
  - Risk factors include older age, male gender, and radiation exposure
- **Natural History**:
  - Distinct phases:
    - Chronic phase – majority of new diagnoses
    - Accelerated phase—increasing blast count to 20% (newer WHO criteria) or 30% (older MDACC criteria, used in prior trials)
    - Blast phase—20% blasts (WHO, newer) or >30% blasts (MDACC), and may manifest as AML or ALL; treated as such
  - Pts may be asymptomatic or experience fatigue, weight loss, night sweats, early satiety.
  - Hepatosplenomegaly, lower sternal tenderness (from expanding bone marrow), and gout can be seen, as well as pruritus and night sweats.
- **Pathophysiology**:
  - Presence of the t(9;22) translocation, resulting in the Philadelphia chr and formation of the BCR-ABL1 fusion gene.
  - The ABL1 oncogene encodes a tyrosine kinase involved in cell differentiation, division, adhesion. Translocation of the ABL1 gene to the breakpoint cluster region (BCR) of chr 22 results in constitutive activation.
- **Diagnosis**:
  - 1) CBC and smear, 2) BM bx, and 3) molecular diagnostics (via karyotype, FISH, RT-PCR) demonstrating BCR-ABL1 fusion gene (At MGH: obtain RT-PCR for BCR-ABL; NOT a qualitative test).
  - RT-PCR is utilized to determine molecular remission and response to therapy.
  - CBC typically shows:
    - Leukocytosis (often WBC > 100k)
    - Thrombocytosis, anemia
    - Differential w/ virtually only neutrophils and myeloid progenitors (blasts < 2%).
    - Basophilia and eosinophilia nearly always seen, has prognostic significance.
  - Cells are morphologically normal, but have low leukocyte alkaline phosphatase (LAP) activity, which distinguishes CML from reactive leukocytosis (leukemoid reaction).
  - % blasts defines the phase of dz (though additional criteria also relevant):
    - Accelerated phase (≥ 1 of the following): 10-30% blasts, leukocytosis, splenomegaly, thrombocytosis, or cytopenia unresponsive to therapy
    - Blast phase: >30% blasts, large foci of blasts on BM bx, extramedullary blastic infiltrates (e.g. chloroma). Can be myeloid (70%) or lymphoid (30%) blast crisis. Additional cytogenetic abnormalities define accelerated phase and blast phase.
- **Treatment and Prognosis**:
  - Chronic phase: tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib). Generally durable responses w/ near normal life expectancy. TKIs cont. indefinitely for most patients.
  - Patients are characterized as (1) low risk or (2) intermediate/high risk based on standard scoring systems (Sokal, Hasford EURO, EUTOS long-term survival)
    - Low-risk: start first-generation (imatinib) or second generation TKI
    - Intermediate/high-risk: start second generation TKI
  - Response to TKI therapy is characterized based on hematologic, cytogenetic, and molecular responses (See Table below)
  - TKIs are well-tolerated but have several common side effects (See below Table of tyrosine kinase inhibitors)
    - All TKIs cause neutropenia and thrombocytopenia
    - Imatinib, dasatinib, bosutinib: Improved GI tolerability w/ food
    - TKI hematologic toxicity management:
    - Manage w/ transient interruptions of TKI therapy and dose modification per package insert.
    - Myeloid growth factors may be used for management of neutropenia.
    - Erythropoiesis-stimulating agents (ES) are not recommended (no impact on OS, ↑ risk for thrombosis)

- BCR-ABL1 kinase domain mutation analysis is often performed for progression, in advanced dz, and if concern for TKI resistance:
  - If T315I mutation noted, ponatinib and asciminib (ABL-001) are the only effective TKIs. Ponatinib notable side effect is ↑ risk of ACS and stroke. Allo-HSCT should be considered.
  - Other ABL1 mutation guide selection of TKI (per NCCN guidelines), but occur infrequently.
- Accelerated/blast phase: prognosis is poor and relapse is high w/ TKI monotherapy. Often considered for HSCT. Patients can progress to myeloid blast crisis (70%) or lymphoid blast crisis (30%) and are treated as AML or ALL w/ TKI.
- Criteria for TKI discontinuation in patients includes TKI duration > 3 yrs and in MR4 for at least 2 yrs. Patients that discontinue TKI need to be closely followed in clinic and therapy is reinstituted at loss of major molecular response (MMR) if PCR >0.1% on IS.

Hematologic, cytogenetic, and molecular response to TKI therapy

Response	Hematologic	Cytogenetic	Molecular
Measure	CBC w/ differential	Karyotype/FISH	RT-PCR
Stage	WBC < 10 Basophils < 5% Plt < 450 Spleen Size ↓	% Ph+ cells (of 20) -None: 95% -Minimal: 66-95 -Minor: 26-65 -Major: 1-35 -Complete: 0	BCR-ABL1 mRNA -MR2 < 1% -MR3 <0.1% -MR4 < 0.01% -MR4.5 < 0.0032%
Expected time after starting therapy	Remission: 1-3 mo.	<95% at 3 mo. <35% at 6 mo. Remission at 1 yr	<10% at 3 mo. <0.1-1% at 1 yr

Tyrosine Kinase Inhibitors

TKI	Dose	Side effects	Pearls/Administration
Imatinib (Gleevec)	400 mg daily Renal, hepatic Adj.	Fluid retention, Chronic fatigue, muscle pain, hepatotoxicity, hypophosphatemia, changes in bone mineral density, hypothyroidism Rare, long term: heart failure	• Moderate emetic potential, antiemetics may be recommended for prevention • Drug interactions: substrate and moderate inhibitor of CYP3A4, inhibitor of 2D6, 2C9 • Caution w/ warfarin
Dasatinib (Sprycel)	100 mg daily No dose Adj.	Fluid retention, pleural/pericardial effusion, GI upset, rash, bleeding (inhibits platelet aggregation) ↑ risk of pericardial/pleural eff: prior cardiac hx, HTN, higher dose (70mg BID) More myelosuppression than imatinib Rare: pulmonary arterial hypertension	• Only TKI that crosses BBB • Contraindicated w/ proton pump inhibitors • If H2 antagonist needed, separate dasatinib 2 hours before or at least 10 hours after • Drug interactions: CYP3A4 substrate • Contraindicated Mutations: T315I/A, F317L/V/I/C, V299L
Niloltinib (Tasigna)	300 mg BID Hepatic Adj.	Black Box: QTc prolongation Headache, pancreatitis, hepatotoxicity, metabolic syndrome, hypophosphatemia Rare: Peripheral arterial occlusive dz	• Administer on empty stomach • Drug interactions: substrate and moderate inhibitor of CYP3A4 • Contraindicated Mutations: T315I, Y253H, E255K/V, F359V/C/I, G250E

Bosutinib (Bosulif)	400 mg daily Renal, hepatic Adj.	Diarrhea, nausea/vomiting, rash, hepatotoxicity	• Avoid acid suppressive therapy, use H2 antagonists if needed • Drug interactions: substrate of CYP3A4 • Contraindicated mutations: T315I, V299L, G250E, F317L
Ponatinib (Iclusig)	45 mg daily Hepatic Adj.	Blackbox: arterial occlusion, VTE, heart failure, hepatotoxicity Rash, dry skin, HTN, pancreatitis, neuropathy, ocular toxicity, hemorrhage, fluid retention, cardiac arrhythmias	• 2nd line tx • Avoid acid suppressive therapy, use H2 antagonists if needed • Drug interactions: substrate of CYP3A4 • Dose reduction (30mg) recommended when co-administered w/ strong CYP3A inhibitors • Contraindicated mutations: None
Asciminib (prev. ABL001), FDA breakthrough desig.	~40 mg BID	Fatigue, hypertension, pancreatitis, rash	• Targets the ABL myristoyl pocket (STAMP), different from other TKI. • 2nd line tx • Effective w/ T315I mutation

Chronic Lymphoid Leukemia (CLL) (NCCN; CLL, v4.2020)

- Overproduction of mature-appearing, but dysfunctional lymphocytes. Small lymphocytic lymphoma (SLL) is often lumped w/ CLL and has similar underlying dz biology.
- **Epidemiology**:
  - 25-30% of leukemia in US adults. Median age at presentation is 70.
  - Risk factors include older age, male gender, white ethnicity, 1st degree relatives w/ CLL
- **Natural History**:
  - Pts often asymptomatic, but can have "B" symptoms of lymphoma: unintentional weight loss, drenching night sweats, fatigue (should raise concern for Richter's transformation)
  - Lymphadenopathy and hepatosplenomegaly commonly seen. CLL cells can infiltrate any organ, such as the skin (leukemic cutis).
  - Can be a/w autoimmune hemolytic anemia or thrombocytopenia, agranulocytosis
  - Survival is highly variable, w/ a subset of patients having similar survival to the general population w/o tx
- **Pathophysiology**:
  - Not entirely understood, but thought to occur a two-step model: 1) abnl antigenic stimulation of B-cells leads to monoclonal B-cell lymphocytosis, 2) a later genetic mutation leads to the accumulation of tumor cells and progression to CLL
- **Diagnosis**:
  - Need (1) CBC w/ differential, (2) peripheral smear, (3) Flow cytometry (for immunophenotype). BM bx is not required for diagnosis.
  - CBC w/ differential will show absolute lymphocyte count (ALC) > 5,000
    - Patient w/ lower ALC can have monoclonal B-lymphocytosis (akin to MGUS, CHIP)
    - Patients may have WBC > 100k w/ mild neutropenia, anemia, thrombocytopenia but are not considered at risk for leukostasis
  - On smear, circulating leukemic cells resemble small, mature lymphocytes
  - Immunophenotype is required for establishing clonality. Circulating cells should express B-cell associated antigens (CD19, CD20, CD23), the T-cell associated antigen CD5, and have weak levels of surface immunoglobulins w/ expression of only a single light chain (kappa or lambda). In rare cases, flow cytometry identifies a biclonal population.
  - Diagnosis: (1) absolute B-cell count ≥ 5k, (2) smear predominantly w/ mature-appearing lymphocytes, and (3) flow cytometry demonstrating clonality of circulating B-cells
  - Other data: (1) Molecular analysis (2) FISH/Karyotype (3) TP53 sequencing

- **Staging**:
  - Rai System: Stage 0 (Low), I-II (Intermediate), III-IV (High Risk). Staging based on extramedullary lymphadenopathy (I), HSM (II), and presence of anemia (III) and thrombocytopenia (IV)
  - Binet System: Stage A-C. Staging based on degree of anemia and thrombocytopenias and # of enlarged areas
  - Lunago: Stage I-IV. Used for SLL staging based on LN spread and if dz is "bulky"
- **Prognosis**:
  - While HCT is the only curative tx for CLL, for many patients, CLL is an indolent dz w/ median survival > 10 yrs. Prolonged remissions w/ current therapies facilitate dying w/ dz rather than of it.
  - Cytogenetic (Karyotype/FISH), Flow Cytometry, and Mutational Analysis results can help to characterize favorable or unfavorable prognosis:
    - Cytogenetics: Unfavorable (del11q, del17p, complex >3 abnormalities); Neutral (normal, +12); Favorable (del13q)
    - Mutations: Unfavorable (TP53 mutated, IGHV <2%); Favorable (TP53 WT, IGHV > 2%)
    - Flow Cytometry: Unfavorable (CD38 < 30%, Zap70 < 20%, CD49d < 30%); Favorable (CD38 > 30, Zap70 > 20, CD49d > 30)
- **Treatment**:
  - Asymptomatic early stage: observation
  - Symptomatic or advanced stage: Decision to treat is triggered by symptoms or complications such as B-symptoms, repeated infections, progressive AIHA or cytopenias
  - Tx regimens also dependent on:
    - Frail OR Age > 65 and younger patients w/ co-morbidities (i.e. CrCl < 70)
    - Presence or absence of TP53 mutation
    - Presence of absence of del(17p)
  - Numerous tx options available based on risk profile and ability to tolerate chemo. Preferred regimens generally include ibrutinib or acalabrutinib (Bruton Tyrosine Kinase or BTK inhibitors) +/- obinutuzumab or rituximab (anti-CD20), venetoclax (anti-BCL2) + obintuzumab (anti-CD20), in addition to several other potential regimens that include rituximab, bendamustine, chlorambucil, fludarabine, etc. Recent studies suggest potency of venetoclax and ibrutinib used in combination.
  - Richter transformation can occur even in patients in a deep remission from CLL standpoint, and is treated like DLBCL w/ R-CHOP, but w/ generally poor outcomes.
  - CAR T cells were initially developed in CLL, w/ effective cures, but not FDA approved presently.

Chronic Myelomonocytic Leukemia (CMML) (NCCN; MDS, v4.2020)

- Characterized by features of both MPN and MDS, occurring most commonly in older adults. Splenomegaly, LAD, nodular cutaneous infiltrates, and paraneoplastic syndromes can be seen. The dz has a variable course and can be aggressive, w/ high risk of progression to AML. Median overall survival is 30 mo.
- **Pathogenesis**: incompletely understood. Deletions or rearrangements of chr 7 and 8 are the most common cytogenetic abnormality, as are recurrent mutations in TET2, RAS, SRSF2, among other genes. Two general subtypes w/ different biology – proliferative and dysplastic.
- **Diagnosis**: CMML is defined by peripheral blood monocytosis (≥10% of WBC count) w/ bone marrow dysplasia in ≥1 myeloid lineage; not meeting criteria for CML, PV, ET; w/ <20% blasts (WHO).
- **Prognosis**: can be estimated by the CPSS-Mol (Blood 2016;128:1408), Mayo Molecular Model (Leuk 2014;28:2206), and others. Typically, ASXL1 mutations and higher WBC/blast counts convey worse prognosis.
- **Treatment**: options are limited, w/ no therapy other than allogeneic-HCT that has been shown to improve survival. Patients may be treated w/ hydroxyurea, hypomethylating agents, and best supportive care. Ruxolitinib (Jakafi) is currently being studied (Blood 2017;130:126), as well as tagraxofusp, a IL3-diptheria toxin conjugate that targets CD123.

Hairy Cell Leukemia (NCCN; HCL, v1.2020)

- Uncommon type of chronic B-cell proliferation, characterized by small mature B-cells w/ lots of cytoplasm and "hairy" projections. Palpable splenomegaly is classic. Symptoms of cytopenia can be seen. Median age of onset is 50-55 y/o and the dz has an indolent course.
- **Pathogenesis**: incompletely understood. Hairy cells are thought to arise from activated memory B cell w/ a BRAF V600E mutation resulting in abnl activation of the RAF-MEK-ERK pathway

- **Diagnosis**: Distinctive morphology and expression of pan-B cell antigens (flow cytometry). BM aspirates are usually dry and show hairy-cells w/ characteristic fried-egg appearance.
- **Prognosis**: Many patients can be observed for mo. to yrs until B-symptoms or worsening cytopenias and splenomegaly develop.
- **Treatment**: Cladribine (2-CDA) is the most common initial therapy a/w high response rate (>75% CR). Other agents include rituximab, pentostatin. There are ongoing trials w/ BRAF V600E directed therapy, and other antibodies targeting CD22, CD25, and others.

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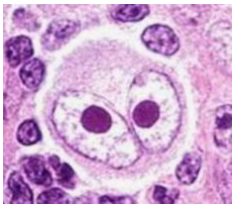
Overview of Lymphoma

- Diverse set of neoplasms arising from B- or T- lymphocytes. They are most commonly found in lymph nodes and other lymphoid organs, but may be found in any location or organ in the body.
- Lymphomas are generally divided into Hodgkin lymphomas and non-Hodgkin lymphomas (NHL), though NHL is a general term comprising over 70 distinct biologic and clinical subtypes*
- 83,000 new cases per year diagnosed in the United States, and 21,000 deaths

* Pasqualucci L, Dalla-Favera R. Molecular Biology of Lymphomas. In: DeVita VT, Lawrence TS, Rosenberg SA. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology.* 10th ed. 2015

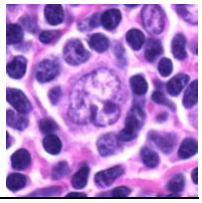
Hodgkin Lymphoma has two subtypes:

(1) Classical HL (CHL)



1. 95% of cases, WHO classification subdivided in 4 histologic subtypes that are managed similarly:
2. **nodular sclerosis (70%)**
3. **mixed cellularity (25%)**
4. **lymphocyte rich (5%)**
5. **lymphocyte depleted (<1%)**
6. All classical HL subtypes are characterized by the presence of large atypical monoclonal lymphoid cells that are mononuclear or multinucleate (**Hodgkin Reed-Sternberg cells,** see figure), but these only constitute about 1% of the overall tumor cellularity. Reed-Sternberg cells are crippled B-cells which do not transcribe immunoglobulins and typically co-express **CD15 and CD30,** but usually **lack typical B-cell markers (CD20, CD45).**
7. The surrounding cellular material is a heterogeneous polyclonal inflammatory cellular infiltrate.

(2) Nodular lymphocyte predominant HL (NLPHL)



1. Has large neoplastic cells known as **LP (lymphocyte predominant) cells** (also known as **L&H** or **"popcorn cells**" [see figure]) in a nodular meshwork of follicular dendritic cell processes.
2. Typical B-cell surface antigens (**CD20, CD45)** are present, and they do not express CD30 or CD15 **(CD15- CD30-).** EBV is rarely present.
3. Similar morphology and identical immunophenotype to T-cell/histiocyte-rich B-cell lymphoma (a variant of diffuse large B-cell lymphoma), which can arise from NLPHL.

Epidemiology

- **Bimodal** distribution of CHL peaking in young adulthood and then rising in the elderly
- Etiology unknown but **association w/ EBV** seen in 30% patients, as well as increased frequency in patients w/ **HIV** infection and who are **immunocompromised**
- NLPHL occurs more frequently in men than in women, and occurs at a median age in the 30s

Clinical Presentation and Dx

- **Painless LAD +/- splenomegaly**
- Systemic **"B" symptoms** of fevers, drenching night sweats, or unintentional weight loss, occur in a significant minority of patients, as well as **pruritus** (in particular CHL), pain in involved lymph nodes upon ingesting alcohol (alcohol induced degranulation of eosinophils).
- Dx made best w/ **excisional lymph node Bx (preferred) or core Bx**

Evaluation and Staging:

- Workup includes LN Bx, CBC w/diff, BMP, LFTs, LDH, albumin, ESR, HIV, PET/CT, fertility counseling. PFTs (if bleomycin planned) and echocardiogram required prior to therapy

Ann Arbor Staging System: *Adapted from Press, OW. Lymphoma. In: Hensley, ML, et al. ASCO-SEP Program. 5th ed.*

Stage	Extent of Dz
I	Involvement of single lymph node region or lymphoid structure
II	Involvement of 2 or more lymph node regions on one side of diaphragm
III	Involvement of 2 or more lymph node regions on both sides of diaphragm
IV	Disseminated involvement of an extranodal site

Each stage has A and B subtypes, designating the absence (A) or presence (B) of B symptoms.
Direct extension from involved lymph node to extranodal site noted by subscript E and does not qualify for stage IV.

Prognosis:
- Early-stage HL: Adverse risk factors include bulky Dz (>10cm diameter or greater than 1/3 mediastinal diameter), elevated ESR, >2-3 sites of nodal Dz, extranodal sites
- Advanced HL: **HL International Prognostic Score (IPS)**: Age >45 yrs, male, stage IV, albumin <4, Hgb < 10.5, WBC ≥15,000, lymphocytes <600 or 8% (J Clin Oncol 2012;30:3383)
- Interim FDG-PET is a good predictor of PFS and permits early detection of suboptimal response

Tx:
- **Tx of CHL:**
  - *Stage I-II*: **2-4 cycles of ABVD** (Adriamycin [doxorubicin], Bleomycin, Vinblastine, Dacarbazine) **+ XRT** *or* w/ 4-6 cycles of **ABVD** alone (Tx depends on presence of bulky Dz and risk strat.), each w/ cure rates of 90-95%. Interim PET/CT imaging is used to guide intensification or de-intensification of therapy based on response.
  - *Stage III-IV*: **PET-adapted therapy w/ 6 cycles of ABVD** (w/ omission of bleomycin after 2 cycles if PET negative, NEJM 2011;365) or 6 cycles of **AVD + brentuximab vedotin** (anti-CD30 antibody conjugated to auristatin E, anti-mitotic tubulin inhibitor**;** ECHELON-1 study Lancet 2015;385)
  - *Relapsed Dz*: Second line combination chemotherapy (e.g. ICE) followed by consolidation w/ high dose therapy and autologous stem cell rescue (**HDT/ASCR**). **Brentuximab vedotin** (AETHERA NEJM 2018;378:331) and immune checkpoint inhibitors (**nivolumab** NEJM 2015;372**, pembrolizumab** Keynote-204) are often effective in patients who relapse after or are not candidates for HDT/ASCR.
- **Tx of NLPHL:** RT for localized Dz. Chemotherapy plus rituximab for advanced stage Dz

Non-Hodgkin Lymphoma

Indolent lymphomas are usually slow growing Blood 2016;127:2375. Asymptomatic patients w/ non-bulky Dz typically followed w/ surveillance alone.
- Tx indicated for bulky/symptomatic Dz, bone marrow impairment, or organ dysfunction.
- Aggressive and highly aggressive lymphomas require therapy soon after Dx w/ multi-agent chemotherapy.

Epidemiology:
- NHLs are the 7th most common type of cancer, and the incidence is stable.
- Most cases are sporadic, though risk is increased in the setting of HIV infection, immune suppression, and autoimmune Dz

Dx and Staging:
- Usually present w/ **painless lymphadenopathy** though a minority will present w/ systemic B symptoms or local symptoms related to compression by tumor
- For Dx **excisional Bx** preferred, FNA w/ high false-negatives, core needle Bx usually acceptable for deep sites of Dz not easily amenable to surgical excision
- **Staging** uses same Ann Arbor system as HL (Lugano modification J Clin Oncol 2014;32:3059) and usually requires PET/CT scans. BM Bx may be required in selected circumstances.

NHLs Organized by Aggressiveness:

Indolent	Aggressive	Highly Aggressive
1. Follicular lymphoma 2. Small lymphocytic lymphoma/Chronic lymphocytic leukemia 3. Marginal zone lymphomas 4. Hairy cell leukemia	1. DLBCL 2. Primary mediastinal large B-cell lymphoma 3. Mantle cell lymphoma 4. Peripheral T-cell lymphomas 5. Anaplastic large B-cell lymphoma	1. Burkitt lymphoma 2. Lymphoblastic lymphoma 3. High grade B NHL NOS 4. High grade B-cell lymphoma w/ translocations of MYC and BCL2 and/or BCL6 5. Adult T-cell leukemia/lymphoma

Overview of the Most Common NHL Subtypes:

Diffuse Large B Cell Lymphoma (DLBCL) and High Grade B-cell Lymphoma (HGBCL)

- DLBCL NOS is the most common NHL, may involve any nodal or extranodal site. Presents over weeks-months, usually w/ local or systemic sxs. Subtyped by cell of origin: germinal center B-cell (GCB) or activated B-cell (ABC) DLBCL.
- HGBCL NOS or HGBCL w/ rearrangements of MYC and BCL2 and/or BCL6: **"double/triple hit,"** may behave as intermediate between DLBCL and Burkitt lymphoma

- International Prognostic Index (**IPI**) used to classify risk (includes age, LDH, performance status, stage, and number of extranodal sites). **CNS-IPI** (IPI risk factors and renal/adrenal involvement) is used for identifying patients at increased risk of CNS relapse who may benefit from CNS prophylaxis w/ high dose systemic MTX or intrathecal MTX
- Early stage Tx: 4-6 cycles **R-CHOP** (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) or 3 cycles of **R-CHOP plus RT**
- Advanced stage Tx: 6 cycles **R-CHOP** (DLBCL) or **R-mini-CHOP** (frail/old) (**NCCN 2020 B-Cell Lymphomas**); double or triple hit and primary mediastinal large B-cell lymphoma treated w/ **da-EPOCH-R**.
- Pts high risk for CNS recurrence are given ppx intrathecal MTX or systemic MTX in addition to R-CHOP
- Relapsed/refractory Dz: 2nd line for transplant-eligible: **R-DHAP, R-ICE, R-GDP, R- R-GemOx** followed by **HDT/ASCR** if chemosensitive (**NCCN 2020 B-Cell Lymphomas**).
- 3rd line: **CAR-T** therapy (anti-CD19): **Yescarta** (Axicabtagene ciloleucel, ZUMA-1 study, **Lancet 2019;20:31**), **Kymriah** (tisagenlecleucel, JULIET study, **NEJM 2019;380**), **Breyanzi** (TRANSCEND, **Lancet 2020;396:839**). Subsequent therapies: polatuzumab vedotin +/- bendamustine +/- rituximab; lenalidomide +/- rituximab (ABC DLBCL), ibrutinib (ABC DLBCL), alternative chemoimmunotherapy.

Follicular Lymphoma (FL)

- 2nd most common lymphoma, paradigm for indolent lymphomas
- Follicular growth pattern on Bx, ***BCL2*** often overexpressed from **t(14;18)** chromosome translocation (>85%)
- Tx: Observation, RT, anti-CD20 **rituximab**, chemoimmunotherapy **w/ BR** (bendamustine plus rituximab), **CHOP,** or **CVP + rituximab** or **obinutuzumab (O)**. O-Chemo followed by O maintenance achieves longer progression-free survival compared w/ rituximab-based therapies. For relapse: Chemoimmunotherapy (O-chemo if R-refractory), **R²** (lenalidomide plus rituximab), PI3Kd inhibitors (**idelalisib**, **duvelisib**, **copanlisib**), or **tazemetostat** (EZH2 inhibitor).
- Approximately 15% of patients will undergo transformation to more aggressive lymphoma

Marginal Zone Lymphomas and Mucosa-associated lymphoid tissue (MALT) Lymphoma

- Three subtypes: Nodal, splenic, and extranodal (also known as mucosa associated lymphoid tissue [MALT] lymphoma). All are indolent lymphomas.
- **MALT** lymphomas can affect GI (stomach most common), respiratory tract, ocular adnexa, salivary glands, thyroid, kidney, prostate, others. Gastric MALT usually H. pylori associated, usually **cured w/ H. pylori eradication** (unless a/w t(11;18)). Tx early stage H. pylori negative or t(11;18): **RT** usually curative. Advanced stage Dz may be treated w/ single-agent rituximab or chemoimmunotherapy.
- **Nodal** marginal zone NHL involves the lymph nodes. Tx early stage: **RT.** Tx of advanced stage Dz: observation, single-agent **rituximab, BR, R-CHOP, R-CVP**.
- **Splenic** marginal zone lymphoma involving spleen, blood, bone marrow, less commonly nodes, sometimes **HCV-associated**. Tx: **antiviral Tx if HCV+**, observation, **splenectomy**, single-agent **rituximab** or chemoimmunotherapy.
- Relapsed/refractory marginal zone lymphomas Tx: w/ single-agent **rituximab**, chemoimmunotherapy, **ibrutinib** (BTK inhibitor), **R²**.

Small lymphocytic Lymphoma (SLL)/Chronic Lymphocytic Leukemia (CLL)

- SLL defined by **presence of nodal or extranodal Dz** *and* < 5000/mm³ of circulating clonal B cells in the blood, CLL ≥ 5000/mm³ of circ. clonal B cells +/- nodal and/or extranodal Dz.
- Fewer than 5000/mm³ of circulating clonal B cells in the blood and no nodal or extranodal sites of Dz is considered not to be malignant and is classified as **monoclonal B-cell lymphocytosis** (MBL, CLL type or non-CLL type). MBL CLL-type has a 1% risk per year of CLL.
- Prognostic variables: FISH (e.g. 17p del, 11q del), NGS (e.g. TP53), IGHV mutation status.
- Tx: Observation, **Venetoclax** (BCL2 inhibitor) + **Obinutuzumab** x 1 year, or BTK inhibitor (**Ibrutinib** or Acalabrutinib) +/- obinutuzumab **NEJM 2019;381:432**, **Lancet 2019;20:43**, **Alliance A041702**, **Lancet 2020;395:1278**, **NEJM 2019;380:2225**). For young/fit pt w/ IGHV mutated p53 wild type CLL: consider **FCR** (fludarabine, cyclophosphamide, rituximab), which is potentially curative. Relapsed/refractory CLL is treated w/ venetoclax +/- rituximab/obinutuzumab, BTKi (ibrutinib or acalabrutinib), PI3Kd inhibitor (idelalisib, duvelisib). Therapy chosen based on del17p, TP53, IGHV (Ig heavy chain variable region) mutation

Mantle Cell Lymphoma (MCL)

- 6% of NHL, a/w t(11;14) (q13;q32) translocation w/ **cyclin D1** overexpression; rare cases of Cyclin D1-negative MCL (typical MCL immunophenotype and SOX11+)
- Vast majority present w/ advanced stage Dz: lymphadenopathy, splenomegaly, extranodal involvement is common (GI tract, blood, bone marrow).
- Highly variable Dz biology; more aggressive course is a/w high risk morphology (e.g. blastoid morphology), TP53 mutation, SOX11 expression, high Ki-67; indolent course is often a/w spleen/blood/marrow presentation, low Ki-67, and lack of SOX11.
- Tx of transplant-eligible patient: rituximab and cytarabine-containing chemoimmunotherapy **(e.g. R-DHAP, Nordic Regimen)** followed by **HDT/ASCR** and **rituximab maintenance**. Tx of transplant-ineligible patient: **BR.** If indolent MCL and asymptomatic w/ low Dz burden: observation. Tx of relapsed/refractory Dz: **BTKi** (ibrutinib, zanubrutinib), **R²**, **venetoclax** (BCL2i). If localized Dz (rare): can consider combined modality therapy. **CAR-T** for relapsed Dz: **Tescartus** (**ZUMA-2**, **NEJM 2020;382:1331**)

Peripheral T-Cell Lymphomas (PTCL)

- Diverse group of T-cell tumors, e.g. PTCL-NOS (most common), anaplastic large cell lymphoma (ALCL), angioimmunoblastic T cell lymphoma (AITL).
- PTCL has median age 60, men>women (2:1), and most pts p/w advanced stage Dz; p/w LAD +/- extranodal Dz.
- Tx: **Brentuximab vedotin + CHP** (cyclophosphamide, doxorubicin, and prednisone) (if CD30+), **CHOP** or **CHOEP** (if CD30-,(**NCCN 2020 T-Cell Lymphomas**), **HDT/ASCR** considered in young fit patients, except for favorable subtypes of ALCL (ALK+ or DUSP22+). Relapsed/refractory Dz treated w/ chemotherapy combinations (e.g. ICE, DHAP, GDP) or targeted agents (e.g. brentuximab vedotin, romidepsin, pralatrexate, belinostat).

Burkitt Lymphoma

- Highly aggressive malignancy w/ high proliferation rate and mature B-cell immunophenotype
- Histology is "starry-sky" pattern of macrophages phagocytosing apoptotic tumor cells. Burkitt lymphoma has translocation of ***c-Myc*.**
- **Endemic** in Africa, where classic presentation is jaw tumor in children and is EBV-associated.
- **Sporadic** cases often present w/ extranodal Dz, most common being ileocecal masses.
- **Immune-deficiency-associated**: HIV infection, most commonly in young men
- High LDH and CNS and/or bone marrow involvement constitute high-risk features.
- TLS and renal failure are potential associations given rapid growth rate (need TLS prophylaxis)
- Tx: **R-CODOX-M/IVAC** includes alternating cycles of R-CODOX-M (rituximab, cyclophosphamide, doxorubicin, vincristine, cytarabine, high dose MTX, intrathecal MTX) and **R-IVAC** (rituximab, ifosfamide, cytarabine, etoposide, and intrathecal MTX). Alternate less intensive regimen is **DA-EPOCH-R + intrathecal MTX.**

Overview

- **Plasma cell dyscrasias:** spectrum of diseases characterized by clonal proliferation of terminally differentiated B cells (**Principles and Practice of Oncology, 11th ed. 2015; p151**). These include monoclonal gammopathy of uncertain significance (MGUS), smoldering myeloma, multiple myeloma (most common), light-chain disease, solitary plasmacytoma and extramedullary plasmacytoma.
- **Multiple myeloma (MM)**: incurable disease characterized by clonal proliferation of plasma cells in the bone marrow, accumulation of monoclonal proteins and associated end organ complications. MM can progress to plasma cell leukemia (PCL) in late stages in 1-4% of cases.
- **Solitary Plasmacytoma**: bx-proven solitary lesion of bone or soft tissue with e/o clonal plasma cells. Normal bone marrow with no e/o clonal plasma cells. Radiation therapy to the involved site at 40 to 50 Gy is given +/- surgery, with clinical monitoring (3-year progression to MM about 10%).
- **Plasma Cell Leukemia:** Aggressive form of myeloma with circulating clonal plasma cells in peripheral blood and extramedullary disease, which is treated with combination chemotherapy.
- **Waldenstrom Macroglobulinemia:** Pathologically and clinically similar to low grade lymphomas. IgM paraprotein is present. Morphology of the neoplastic cells is referred to as "lymphoplasmacytic."
- **POEMS Syndrome**: Characterized by polyneuropathy, organomegaly, endocrinopathy (hypogonadism in 70% of males), M protein, and skin changes, usually with either osteosclerotic bone lesions or Castleman disease.
- **Immunoglobulin AL Amyloidosis**: An uncommon consequence of clonal plasma cell disorders and affects numerous organs (systemic disease). Concurrent with myeloma only in ~10% of patients.

Multiple Myeloma

Presentation

- Defining clinical features: CRAB (hyperCalcemia, Renal failure, Anemia, and Bone disease)
- Roughly 80% of MM is thought to originate from non-IgM MGUS with progression to smoldering myeloma and eventually MM (**Lancet Oncol 2014;15:e538**).
- IgM MGUS usually progresses to Waldenstrom macroglobulinemia.

Epidemiology

- Incidence: 7 per 100,000 annually (MGUS is present in about 3-4% of pop. > 50yo).
- Median age at dx: 65yo. 2-3x more common in Black compared to White pop.
- Median survival: 5-7 yrs, though course varies significantly.
- Possible environ. risk factors: farming (?pesticides), hair dyes, benzene, and

Pathophysiology

- MGUS is a premalignant, asymptomatic precursor dz to MM. MGUS likely begins from antigenic stimulation → abnl response + development of abnl cytogenetics.
- Common MGUS cytogenetic abnormalities are reciprocal translocation of immunoglobulin heavy chain (IgH) locus on chromosome 14q32 and 1 of 5 recurrent partner chromosome loci. Trisomies and hyperdiploidy ~50%.
- Following dev. of MGUS clone, the two-hit genetic model of malignancy leads to MM. Specific steps are unknown, though further somatic mutations, CNVs, and alterations in methylation and micro-RNA are a/w progression to MM.
- The MGUS to MM transition also often involves an augmentation of receptor activator of NF-kappaB ligand (RANKL) expression by osteoblasts and reduction of osteoprotegerin (OPG) level, its decoy receptor. **Increase in the RANKL/OPG ratio** is key for osteoclast activation.
- Other factors also play a role in **increasing** osteoclast activity (MIP-1-alpha, SDF-alpha, IL-3, IL-1 beta, IL-6) and **inhibiting** osteoblast differentiation (IL-3, IL-7, DKK1) → osteolytic bone dz.

Diagnosis:

- Labs: Serum protein electrophoresis (SPEP), serum immunofixation (SIFE), serum free light chains (SFLC), urine protein electrophoresis (UPEP), and urine immunofixation (UIFE). SFLC can be used in place of urine studies but if monoclonal plasma disorder identified, urine studies are required. Some patients (<3%) have oligosecretory or nonsecretory myeloma.
- Additional labs: CBC, Cr, Ca, beta-2 microglobulin, albumin, LDH, bone marrow aspiration and biopsy.
- Myeloma cells usually stain + for CD38, CD56, and CD138. Cytogenetics and molecular diagnostics are utilized for risk stratification.
- Imaging: Skeletal survey replaced by whole body low-dose CT scans. Whole-body MRI and/or FDG-PET combined w/ CT may also be performed.
- Monitoring of therapy: CBC, Cr, Ca, M protein via SPEP/UPEP; for oligosecretory or nonsecretory myeloma, SFLC assay, radiographic studies, beta-2 microglobulin and/or bone marrow may be used.

Condition	Diagnostic Criteria	Progression to MM
Non-IgM MGUS	- Serum monoclonal protein <30 g/L - Clonal BM plasma cells <10% - No end-organ damage (i.e., CRAB or amyloidosis)	1%/yr
IgM MGUS	- Serum IgM monoclonal protein <30 g/L - Clonal BM lymphoplasmacytic/plasma cells <10% - No end-organ damage, constitutional sx, hyperviscosity, LAD/HSM	1.5%/yr*
Light-chain MGUS	- Abnml FLC ratio (<0.26 or >1.65) and ↑ level of appropriate light chain - Clonal BM plasma cells <10% - Urinary monoclonpal protein <500 mg/24hr - No end-organ damage (i.e., CRAB or amyloidosis)	0.3%/yr
Smoldering myeloma	- Serum monoclonal protein (IgG or IgA) ≥ 30 g/L or urinary monoclonal protein ≥ 500 mg/24hr and/or clonal BM plasma cells 10-60% - Absence of myeloma-defining events or amyloidosis	10%/yr
Multiple myeloma	- Clonal BM plasma cells ≥ 10% OR biopsy-proven bony or extramedullary plasmacytoma - ≥1 myeloma-defining event(s): 1. Evidence of related end-organ damage: a. Serum calcium >1mg/dL higher than ULN or >11mg/dL b. CrCl <40mL/min or serum Cr >2mg/dL c. Hgb >2g/dL lower than LLN or Hgb < 10g/dL d. ≥1 osteolytic lesions on skeletal XR, CT, or PET-CT (if <10% clonal plasma cells on bone marrow, >1 lesion required) 2. Clonal BM plasma cells ≥ 60% 3. Involved/uninvolved serum FLC ratio ≥ 100 4. >1 focal lesion on MRI (each 5mm or more)	N/A
(Adapted from Rajkumar SV et al. International Myeloma Working Group Lancet Oncol. 2014) *Progression to smoldering and symptomatic Waldenstrom (and infrequently to IgM MM).		

Prognosis and Staging:

- Patient-related factors: age, comorbidities, performance status.
- Labs: LDH, albumin, beta-2-microglobulin (β2M) incorporated
- Cytogenetics and molecular diagnostics: t(4;14), t(14;16), t(14:20), amp1q, del17p13 (TP53). "Double-hit" with 2 cytogenetic abnormalities has very poor prognosis.
- Other clinical factors: tumor burden, extramedullary dz, circulating plasma cells.
- SMM may be further risk-stratified with **Mayo 20/2/20 criteria** (BM PCs >20%, M spike >2g/L, SFLC >20)(**Blood Cancer J 2018;8:59**).

R-ISS Stage	Features
Stage I	- Serum albumin >3.5 g/dL - Serum β2M <3.5 mg/L - Normal LDH - No high-risk cytogenetics
Stage II	- Neither Stage I or III criteria met
Stage III	- Serum β2M >5.5mg/L - High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] OR elevated LDH
Adapted from: Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk stratification and management (**Am J Hematol 2020;95:548**).	

- Some of the above lab and cytogenetic features are incorporated into the revised international staging system (R-ISS) (**Blood Cancer J 2018;8:59**).

Treatment (Blood Cancer J 2018;8:59)(NCCN MM v2.2019):
Initial therapy depends upon stem cell transplant (SCT) eligibility and risk stratification.

- Regimens with toxicity towards stem cells (i.e., alkylating agents) should be avoided in potential SCT candidates.
- Triplet therapy, combining a proteasome inhibitor, immunomodulator and dexamethasone, is generally the first-line therapy.
- Quadruplet regimens, containing daratumumab, are showing promise. Currently, it is restricted to SCT-eligible patients with high-risk double- or triple-hit MM.

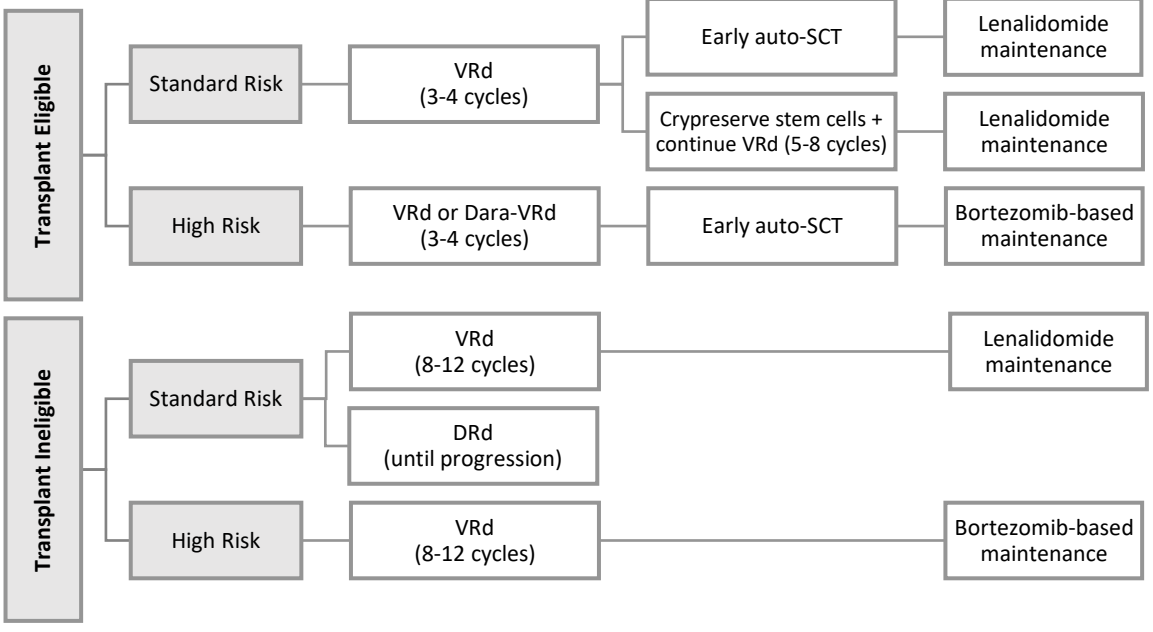
Patients who are SCT candidates:

- Initial therapy: bortezomib, lenalidomide, and dexamethasone (VRd), usually for 3-4 cycles
  - Bortezomib, cyclophosphamide, dexamethasone (VCd) often preferred in renal failure
  - Carfilzomib, revlimid and dexamethasone (KRd) under investigation
- Stem Cell Transplant: predominantly auto-SCT; rarely allogeneic.
  - Median survival is prolonged by about 12 mo. with auto-SCT (NEJM 2017;376:1311). Never curative.
  - Peripheral blood should be harvested after 3 to 4 cycles of induction.
  - Typical conditioning is melphalan monotherapy. Evidence emerging for the addition of busulfan to melphalan in high-risk patients (Blood Adv 2020;:4834).
  - May consider tandem auto-SCT (planned 2nd course of therapy and SCT within 6 mos of 1st) in high risk disease (discrepant trial results in US and Europe).
- Maintenance therapy: lenalidomide and/or bortezomib for at least 2yrs, based on risk. Post-SCT maintenance improves OS but ↑ risk of secondary malignancies like acute myeloid leukemia.

Patients who are not SCT candidates:

- Initial therapy: bortezomib, lenalidomide, and dexamethasone (VRd), usually for 8-12 cycles
  - Bortezomib, cyclophosphamide, dexamethasone (VCd) often preferred in renal failure
  - Lenalidomide plus low-dose dexamethasone (Rd) is preferred in elderly/frail pts
  - Daratumumab in initial regimen likely improves response and PFS (NEJM 2018;378:518)
- Maintenance therapy: lenalidomide and/or bortezomib following initial therapy, based on risk

Treatment approach to newly diagnosed multiple myeloma by transplant elgibility and risk. (Adapted from: Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk stratification and management (Am J Hematol 2020;95:548).



Treatment of Progressive/Relapsed Disease

- A large number of secondary therapies exist using combinations of the drugs described in Table 3. Best regimen depends on individual patient/disease characteristics, drug tox, and prior treatments.
  - Proteasome inhibitor/Immune modulator/Steroid combos: VRd, KRd, IRd, Kd, PVd, etc
  - Combinations may also include monoclonal antibodies like daratumumab, elotuzumab, the HDAC inhibitor panobinostat, the XPO1 inhibitor Selinexor, and/or conventional chemo
- Common scenarios for first relapse (**Blood Cancer J 2018;8:59**):
  - Not refractory to lenalidomide → DRd (preferred); KRd, ERd, IRd (alternatives)
  - Refractory to lenalidomide → DVd (preferred); DPd, IsaPd, KPd, EPd (alternatives)
- A second auto-SCT can be considered for those with remission lasting >24 mos w/ initial auto-SCT; allo-SCT may also be considered but uncommon.
- Novel Therapies
  - Iberdomide and avadomide, novel thalidomide analogs (NCT02773030, NCT01421524)
  - Melphalan-flufenamide (melflufan), alkylating agent (OCEAN trial)
  - Venetoclax, a Bcl-2 inhibitor (BELLINI trial), especially effective in t(11;14) patients.
  - Felzartamab, an anti-CD38 Ab (NCT01421186, NCT03952091)
  - Isatuximab, an anti-CD38 Ab (ICARIA-MM trial)
  - Belantamab mafodotin-blmf, an antibody-drug conjugate (DREAMM-2 trial; common and severe eye toxicity)
  - Anti-B-cell maturation antigen (BCMA) CAR-T cell therapy, idecabtagene vicleucel (KarMMa trial PFS ~12 months, however no effective cures; approved by FDA in Mar 2021)
  - AMG 420, anti-BCME bispecific T-cell engager (NCT03836053)

Therapy	Mechanism	Notable Toxicities
Proteasome Inhibitors Bortezomib (Velcade, V) Carfilzomib (Kyprolis, K) Ixazomib (Ninlaro, I)	Inhibits ubiquitin proteasome pathway -> disrupted protein homeostasis -> apoptosis	Peripheral neuropathy Hepatotoxicity Viral reactivation (ppx w acyclovir/famvir)
Immunomodulatory Drugs Thalidomide (T) Lenalidomide (Revlimid, R) Pomalidomide (Pomalyst, P)	Increased IL-2, cytotoxic T-cell activation; Cereblon inhibition disrupts MYC signal cascade	Thrombosis (ppx aspirin) Cytopenias Teratogens
Monoclonal Antibodies Daratumumab (Darzalex, D) Elotuzumab (Empliciti, E)	 Anti-CD38 Anti-SLAMF7	 Type & screen interference No specific tox noted
Alkylating agents Cyclophosphamide (Cytoxan, C) Melphalan Bendamustine	Inhibit DNA repair, generate crosslinks that inhibit DNA strand separation	Bone marrow suppression, Inc risk of MDS/AML, Hemorrhagic cystitis (cyclophos), pulm tox
Other Panobinostat (Farydak) Dexamethasone (d) - usually 40 mg given on weekly basis	HDAC inhibitor (opens chromatin, multiple effects) Binds corticosteroid receptors, modulates immune system	Severe diarrhea, cardiac ischemia, arrhythmia Standard steroid tox; higher mortality w frequent dosing

Management of disease/therapy complications:

- **Bone disease:** All patients with MM should receive bisphosphonates or denosumab along with calcium/Vitamin D to prevent bone disease
  - Bisphosphonates first-line; reduce progression of lytic lesions and decrease fractures
  - Denosumab, an antibody targeting RANKL, should be considered in renal insufficiency (**Lancet Oncol 2018;19:370**)
- **Infection**: high risk of sepsis 2/2 encapsulated organisms (low functional Igs) and neutropenia
  - All patients should get pneumococcal vaccines
  - Consider IVIg in patients with recurrent bacterial infections
  - Patients on proteasome inhibitors should receive viral ppx (acyclovir/famvir)
  - Some debate over antibiotic prophylaxis (e.g. levofloxacin) during induction

- **Thrombosis**: Full dose aspirin is recommended with immunomodulator-based therapy.
- **Anemia**: ESAs (erythropoietin stimulating agents) vs transfusions
- **Myeloma kidney**: most commonly due to light chain nephropathy; focus on anti-MM therapy to reduce light chain production, addressing reversible causes and bridging with dialysis as needed
    - Anti-MM Tx: preferably cyclophosphamide, bortezomib, decadron (CyBorD). Immunomodulators avoided in renal insufficiency
    - Give IVF to maintain UOP > 3L per day
    - Avoid loop diuretics (may precipitate cast nephropathy), unless needed for hyperCa
    - Plasmapheresis may be considered to remove light chains

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Overview

- Myelodysplastic syndromes (MDS) are cancers of hematopoietic progenitors characterized by bone marrow (BM) failure, clonal expansion, abnl cellular maturation, and the risk of progression to acute myeloid leukemia.
- MDS shares clinical/pathologic features w/ AML but has lower %blasts in peripheral blood and BM (by definition, <20%)
- Prognosis is highly variable, depending on clinical factors, cytogenetics and BM involvement.
- Treatment: Prognosis-dependent: (1) low-risk pts are managed w/ supportive care, (2) high-risk pts are treated w/ goal of decreasing mortality and transformation to AML.

Epidemiology:

- Incidence: 4 to 7 cases per 100,000 persons per year in the U.S. Up to 20 cases/100,000 in pts above 70 y/o
- Median age at dx: 65-75 y/o. Onset < 50 y/o is rare, unless it is therapy-related MDS.
- Risk factors:
  - Advanced age, male gender
  - Environmental exposures (e.g. benzene, tobacco, insecticides)
  - Therapy-related (e.g. prior chemo, radiation)
  - Inherited genetic conditions (Down syndrome, Diamond-Blackfan, Fanconi, Li-Fraumeni)

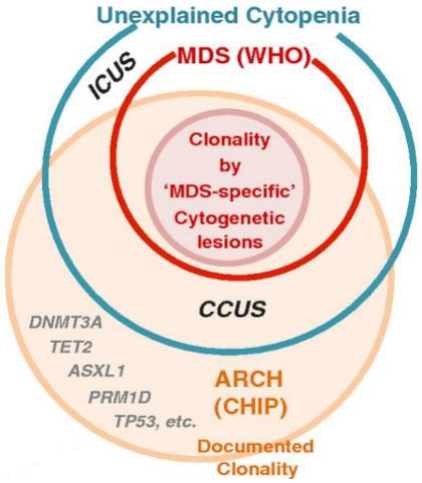
Natural History:

- Pts are often asymptomatic w/ cytopenia found incidentally on routine CBC. Most common clinical feature is signs of anemia (fatigue, exercise intolerance, malaise). HSM and LAD rare and may represent overlap features (e.g., MDS/MPN).
- Dysplastic neutrophils and platelets can lead to infections or bleeding, respectively, out of proportion to neutropenia/thrombocytopenia
- A/w autoimmune dz: chronic rheumatic heart dz, RA, vasculitis, seronegative arthritis, Sweet syndrome (heralds transformation to acute leukemia), others
- Median survival: Widely variable, ranging from <1 year to >10 (see Prognosis section)
- Cause of death: (1) marrow failure (infection most common) or (2) progression to AML

Pathophysiology:

- MDS is distinguished by 3 features: 1) clonality, 2) dysplasia, 3) cytopenias
  - A single hematopoietic progenitor cell inherits or acquires driver mutations, which enables the progenitor cell to undergo clonal expansion, but w/ dysplastic and dysfunctional progeny
  - The dysplastic progeny (i.e. blasts) have a clonal advantage over healthy BM progenitors, possibly through microenvironment interactions → ineffective hematopoiesis and cytopenias
  - MDS is considered to have transformed to AML when BM blast ≥ 20%
  - Clonality is currently assessed in MDS through cytogenetic and molecular testing
- **Cytogenetic mutations** are recurrent chromosomal abnormalities (~50% of pts)
  - Unbalanced abnormalities: del(5q), del(7q), del(20q), loss of Y are most common
  - Balanced abnormalities: t(11;16)(q23.3;p13.3), t(3;21)(q26.2;q22.1), and others
  - Some alterations are diagnostic of MDS in the setting of supporting clinical features (**Blood 2016;127:2391**)
- **Somatic mutations** are single-gene mutations (>90% of MDS pts), typically identified through next-generation sequencing and increasingly important for diagnosis and prognosis
  - Epigenetic modifiers: TET2, IDH1, IDH2, DNMT3, ASXL1
  - RNA splicing machinery: SF3B1, SRSF2, U2AF35, ZRSR2
  - Signaling pathways: RUNX1, KRAS, NRAS, FLT3
  - DNA damage response: TP53

- Improved gene sequencing has resulted in the identification of additional, interrelated hematologic entities w/ permutations of findings (cytopenia ± clonality ± morphologic dysplasia)



Adapted from Ogawa S, Blood 2016;128:337

Comparison of myeloid disorders

	ICUS	CHIP	CCUS	MDS	AML
Clonality	-	+	+	+	+
Dysplasia	-	-	-	+	+
Cytopenia	+	-	+	+	+
BM Blast	< 5%	<5%	<5%	<19%	≥20%

Source: Adapted from Steensma DP, et al., Blood 2015;126:9. Abbreviations delineated below.

  - **CHIP** (Clonal Hematopoiesis of Indeterminate Potential): Defined by presence of mutations typically mutated in myeloid dz, but w/o dysplasia or cytopenia. Risk factor for MDS and other hematologic malignancy. Rate of progression to malignancy is ~0.5%-1% per year, but higher w/ atherosclerotic cardiac dz (NEJM 2017;377:111).
  - **ICUS** (Idiopathic Cytopenia of Unknown Significance): Single or multiple cytopenias, not found to have a clear underlying cause, w/o clonality or diagnostic e/o MDS
  - **CCUS** (Clonal Cytopenia of Unknown Significance): Single or multiple cytopenias w/ a clonal mutation but w/o dysplasia.

Evaluation and Diagnosis:

Diagnostic tools for MDS

	Definition	Source of data
Cytopenia	≥1 of the following: Hgb <10; ANC <1.8; Plt <100k	CBC w/ diff
Dysplasia	≥10% dysplastic cells in any of the erythroid, myeloid, or megakaryocyte lineages	BM Bx or blood smear
% Blasts	<20% of all nucleated BM cells (≥20% meets criteria or AML) on BM aspirate	BM Bx
Cytogenetics	Certain cytogenetic abnormalities are MDS-defining in the appropriate clinical context regardless of whether dysplasia is present (e.g. del(5q)). Others require dysplasia (+8, -Y, del(20q)). Often classified by IPSS-R (see Prognosis section)	Most commonly karyotype and FISH
*Must exclude other causes of cytopenia (e.g. sepsis, nutritional deficiencies, CKD, autoimmune)		

The following cytogenetics exclude MDS and are diagnostic of AML: t(8;21)(q22;q22), RUNX1-RUNX1T1; inv(16)(p13.1q22) or t(16;16)(p13.1;q22), CBFB-MYH11; t(15;17)(q22;q21.1), PML-RARA

Initial Evaluation of Suspected MDS:

- CBC w/ differential, peripheral smear
- BM bx and aspiration w/ iron stain to evaluate for ring sideroblasts
- Cytogenetics (karyotype) +/- genetic sequencing for somatic mutations (Heme SnapShot at MGH)
- Serum EPO level, Folate, B12, iron studies, HIV, TSH, Copper level
- Consider Flow Cytometry to evaluate for PNH and Large Granular Lymphocytic Leukemia

2016 WHO Classification of MDS (Blood 2016;127:2391)

Subtype	Blood Characteristics	Bone Marrow Characteristics
MDS w/ isolated del(5q)	Hgb, Plt nl or increased	Erythroid dysplasia, <5% blasts
MDS w/ ringed sideroblasts	Hgb decreased	Erythroid precursors w/ ring sideroblasts (>15%); or >5% if SFSB1; <5% blasts

MDS w/: single lineage dysplasia (SLD) multilineage dysplasia (MLD)	Cytopenia(s) (both) Monocytopenia (MLD)	Dysplasia > 10% in 1 (SLD) or 2+ (MLD) lineages; <5 % blasts; <15% ring sideroblasts or <5% RS if SFSB1 (MLD)
MDS w/: Excess blasts-1 (EB-1) Excess blasts-2 (EB-2)	Cytopenia(s) (both) monocytoenia (both) 2-4% (1); 5-19% (2) blasts	Dysplasia in 1+ lineage; 5-9% (EB-1) or 10-19% (EB-2) blasts; +/- Auer rods (EB-2)

Prognosis:
Major prognostic factors include 1) number and depth of cytopenias, 2) % BM blasts, and 3) cytogenetics. More recently, somatic mutations are being considered in tx. See tables below. Risk assessment based on these criteria guides tx approaches.

Cytogenetics: Risk stratified according to IPSS-R (see below about IPSS-R).

	Cytogenic profile
Very good	del(11q), -Y
Good	Normal, del(20q), del(5q) alone or double, del(12p)
Intermediate	del(7q), +8, +19, i(17q), other single or double independent clones
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), 3 abnormalities
Very poor	>3 abnormalities

Somatic mutations (NEJM 2011;364:2496): The role of specific mutations continues to evolve.

Mutation	Characteristics
SFSB1	A/w ring sideroblasts subtype and more indolent dz
TET2	A/w slightly improved response to hypomethylating agents (HMA)
ASXL1, RUNX1, EZH2, ETV6, TP53	A/w poor outcomes

IPSS (International Prognostic Scoring System) and IPSS-R (IPSS-Revised):

- Incorporates number/depth of cytopenias, cytogenetics, BM blasts, and age to calculates a score that places pts in risk categories.
- IPSS-R is newer, but trials and existing data are largely based on IPSS. IPSS categories include Low, Int-1, Int-2, and High. IPSS-R categories range from Very Low to Very High.
- Of note, these risk models do not incorporate somatic mutations, though the molecular IPSS-R model (mol-IPSS-R) now offers a dynamic model for taking mutations into account. For IPSS-R calculator, visit https://www.mds-foundation.org/ipss-r-calculator/.

IPSS-R median survival related to age (years)

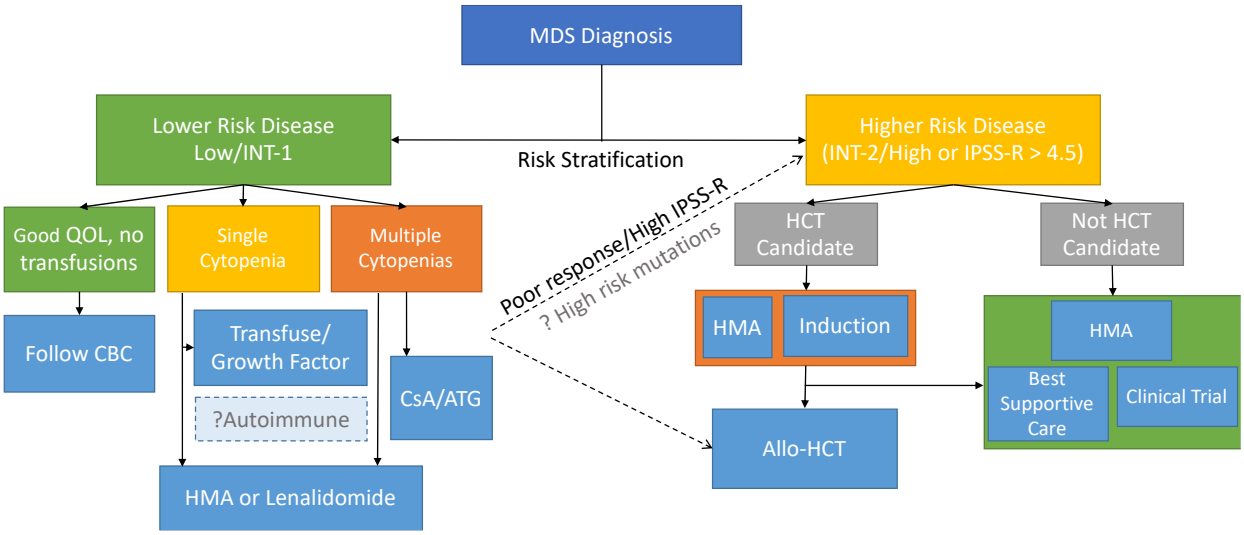
	Very Low	Low	Intermediate	High	Very High
Age ≤ 60	8.8	5.3	3	1.6	0.8
> 60-70	10.2	6.1	3.3	1.6	0.8
> 70- 80	7.0	4.7	2.7	1.5	0.7
> 80	5.2	3.2	1.8	1.5	0.7
AML/25%*	NR	10.8	3.2	1.4	0.7

*AML/25% denotes median time to 25% AML evolution.
Adapted from Greenberg et al, Blood 2012

Treatment (Blood 2006;108:419) (see **NCCN 2021 MDS Guidelines**):

- Therapeutic approach depends on dz risk. Risks below are approximated by IPSS-R.
- Response is based on the IWG (International Working Group) criteria (**NCCN: MDS, v2.2020**)
  - Complete remission (CR): <5% BM blasts, no dysplasia or cytopenias
  - Partial remission (PR): BM blasts ↓ by ≥ 50% but absolute BM blasts still > 5%, no dysplasia or cytopenias
  - Marrow CR (mCR): <5% BM blasts, but still w/ dysplasia or cytopenias. Noted w/ or w/o hematologic improvement.
  - Hematologic improvement (HI): Improved cytopenias characterized by lineage: erythroid (HI-E), platelet (HI-P), and neutrophil (HI-N)

MDS management algorithm (Adapted from Brunner et al, Clin Adv Hematol Oncol 2018;16:56)



- **Very Low/Low/Intermediate (IPSS-R≤3.5) risk pts**: Goal is to reduce symptoms related to specific cytopenias and minimize transfusion requirements:
  - First line: Observation until symptomatic cytopenia or transfusion requirements
  - Manage Anemia:
    - IF Del(5q): Start Lenalidomide (thalidomide analogue): specifically FDA-approved for pts w/ low/INT-1 risk MDS, who are transfusion dependent, and have isolated del(5q). It modulates E3 ubiquitin ligase to CK1α, which preferentially affects del(5q) cells.
    - IF NO Del (5q): check EPO level
      - If EPO < 500, Treat w/ Erythropoietin Stimulating Agent (ESA)
      - If EPO > 500, Consider tx per intermediate/high risk, such as hypomethylating agent (HMA), immunosuppressive therapy (ATG + cyclosporine A), or clinical trial
    - IF MDS w/ Ring Sideroblasts: Consider Luspatercept[10]
  - Manage Thrombocytopenia: TPO agonists (romiplostim, eltrombopag) decrease transfusion requirements and bleeding and should be considered; however, MDS blasts can express TPO receptors, and increases in BM blast % w/ TPO-mimetics have been described. Paradoxically eltrombopag can worsen thrombocytopenia if given w/ HMAs, and has an FDA black box warning due to worsened platelets in a randomized trial.
  - Manage Neutropenia: G-CSF if infectious complications; no known benefit to prophylaxis

- **Intermediate (IPSS-R>3.5)/High/Very High risk (or lower risk pts who progress)**: Goal is dz modification to prevent transformation to AML and improve survival. Selecting the appropriate timing for HSCT is a major consideration. Transplant remains the only curative approach (J Clin Oncol 2011;2:3322).
  - Hypomethylating agents (HMAs) such as azacitidine and decitabine. Since MDS is characterized by a hypermethylated state, HMAs are thought to resume gene transcription by decreasing global methylation.
    - Prolongs time to AML progression compared to conventional chemo or supportive care. Multiple cycles may be given (90% respond by 6mo of therapy), often while preparing for HSCT, or in an ongoing fashion indefinitely for non-transplant candidates
    - Only ~40% of pts respond to HMA (CR, PR, mCR, HI) and response is lost in the majority of pts in 1-1.5 yrs. Median overall survival following HMA failure is poor, estimated to be <6 mo (NEJM 2020;382:140).
  - Allogeneic stem cell transplant: The only curative therapy for MDS, but w/ significant up-front risks (GVHD, infections, relapse, death)
    - Preceded by myeloablative or reduced intensity conditioning.
    - Limited by age (particularly > 70) and comorbidities. Those who are not eligible for HSCT are encouraged to seek clinical trials.
    - Somatic mutations in certain genes (TP53, TET2, DNMT3A) have been shown to be a/w shorter survival following transplant (Haematologica 2014;99:956)(NEJM 2017;376:536).

- Other therapies
  - AML-like induction therapy: Cytarabine and Anthracycline (i.e. "7+3") particularly for those that are young w/ higher blast counts.
  - Immunosuppressive therapy: ATG, cyclosporine. Effective in hypoplastic MDS.
  - For pts w/ IDH1 or IDH2 mutations, consider ivosidenib or enasidenib (FDA-approved for relapsed or refractory AML in pts w/ mutations of these genes) though their role in managing MDS is yet to be fully eval.

- **Cardiovascular risk factor management**
  - Pts w/ MDS and CHIP are at higher risk of death from cardiovascular causes than age-matched controls (**Blood Adv 2017;1:2032**)(**NEJM 2017;377:111**).
  - No formal recommendations have been developed for MDS population; at min. pts should undergo standard screening and management for hypertension, diabetes, hyperlipidemia and CAD risk and be treated accordingly.

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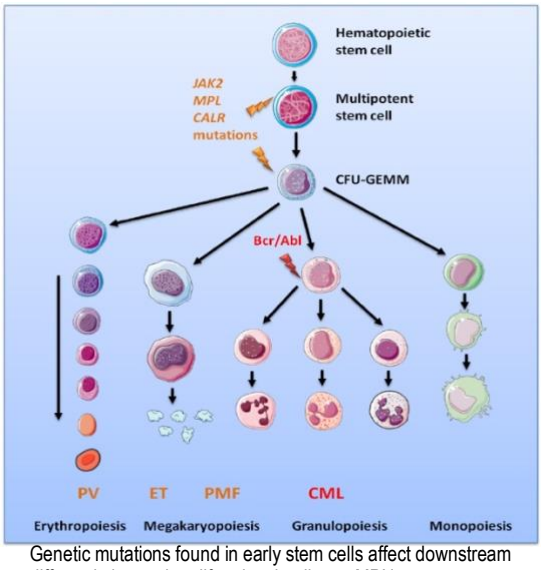
Overview

Myeloproliferative Neoplasms (MPNs) are stem-cell neoplasms w/ shared mutations that constitutively activate the JAK-STAT signaling pathway. The three classic Philadelphia-negative MPNs are:

Polycythemia Vera (PV)	↑↑ Erythrocyte
Essential Thrombocythemia (ET)	↑↑ Platelet
Myelofibrosis (MF, PMF)	Marrow Fibrosis

While each MPN has specific dx criteria, there is overlap in genotype and phenotype. Evolution from one MPN to another is also possible.



Genetic mutations found in early stem cells affect downstream differentiation and proliferation, leading to MPNs.

Pathophysiology of MPNs:

- Phenotypic drivers: JAK2, CALR, MPL
  - Found in the vast majority of MPNs, all activate JAK-STAT signaling, driving cellular proliferation and leading to constitutional symptoms.
  - While certain gene mutations are a/w certain MPNs, they cannot rule in or rule out any MPN.
- JAK/STAT signaling cascade: EPO binding -> dimerization of the EPO receptor, enabling JAK2 to bind the cytoplasmic domain -> phosphorylates and activates several targets including downstream signaling molecule STAT.
  - JAK2, CALR, and MPL mutations enable EPO-independent JAK/STAT pathway activation.
- All MPNs share thrombosis risk, and can also have very significant systemic symptoms
- MPN-SAF: 10-point symptom assessment form, helps measure symptoms overtime, determine therapy needs, and monitor response

Essential Thrombocytosis (ET)

Epidemiology:

- Incidence: Estimated to be 1-2.5 per 100,000
- Median age of dx: 60 yrs. 20% of cases diagnosed < 40 y/o.
- Risk factors: Female, black, older age. Autosomal dominant familial ET have been rarely described.

Natural History:

- Often incidental finding of thrombocytosis. Physical exam often normal, LAD and splenomegaly uncommon. Can be a/w spontaneous abortions (1st trimester)
- Most patients have normal life expectancy (Am J Med 2004;117:755)(Blood 2014;124:2507)
- Cause of death typically cardiovascular (thrombosis) or transformation to post-MPN myelofibrosis (10% at 10 yrs.), to accelerated phase, and to acute leukemia (<3% in 10 yrs).

Symptoms and complications of ET

	Symptom	Risk Factor
Vasomotor (microvascular)	HA, lightheadedness, syncope, acral paresthesia, erythromelalgia, transient vision changes	
Thrombosis	CVA, MI, SVT, DVT, PE	Age > 60, CV RFs, WBC > 11, JAK2 V617 mutation
Hemorrhage*		Plt > 1 million

*From acquired vWD from ↑ protease activity and adsorption of vWD multimers out of circulation

Pathophysiology:

- Thrombocytosis from clonal expansion and ↑ platelet production, not ↑ survival.
- 90% of cases have an acquired mutation: JAK2 (60-65%), CALR (calreticulin, 20-25%), or MPL (myeloproliferative leukemia virus oncogene, 5%). 10-15% have triple negative dz.
- Activating mutations in TPO have been described in familial forms.

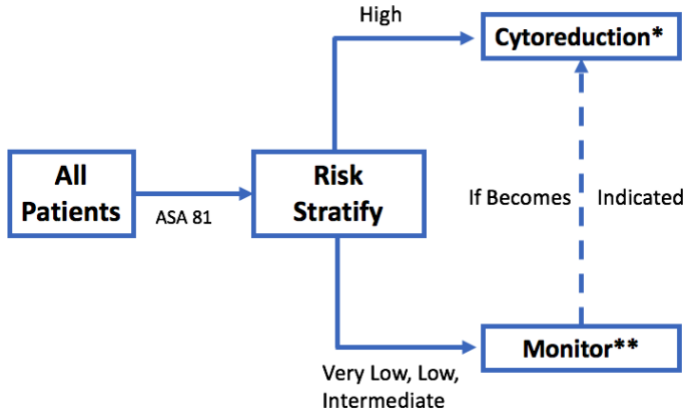
Diagnosis:
Per 2016 WHO Guidelines: need all 4 major criteria or first 3 major criteria plus the minor criterion

Major	Platelets > 450k
	BM bx showing enlarged, mature megakaryocytes w/ hyperlobulated nuclei w/o fibrosis
	Not meeting criteria for BCR-ABL+ CML, PV, PMF, MDS, or other myeloid neoplasms
	Presence of JAK2, CALR, MPL mutations
Minor	Presence of other clonal markers (ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SR3B1)
	No alternative explanation for thrombocytosis

Workup:
1. Repeat CBC w/ differential
2. Peripheral blood smear: should see thrombocytosis, w/ platelet anisocytosis
3. BM bx and aspirate for cytogenetics and molecular testing (elevated platelets alone don't equal ET, a marrow can distinguish from pre-fibrotic myelofibrosis and overt myelofibrosis).
4. If Plt > 1 million, or abnl bleeding (particularly mucocutaneous), assess for acquired vWD.
5. Consider RT-PCR for BCR-ABL1 to exclude CML.

Prognosis:
- Outcomes are worse for those w/ (1) advanced age, (2) h/o thrombotic complications, (3) CV risk factors, and (4) presence of JAK2 mutation
- Scoring system: R-IPSET-Thrombosis (Revised International Prognostic Score for Thrombosis in Essential Thrombocytopenia), used to determine who warrants cytoreduction (**Blood 2012;120:5128**)
  - High-risk: Age > 60 + JAK2 OR h/o thrombosis (at any age)
  - Intermediate-risk: Age > 60 + NO JAK2 + NO h/o thrombosis
  - Low-risk: Age ≤ 60 + JAK2 + NO h/o thrombosis
  - Very low-risk: Age ≤ 60 + NO JAK2 + NO h/o thrombosis
- MPN Personalized Risk Calculator: for predicting overall survival, event-free survival, risk of progression to AML or MF; applies to all MPNs; risk stratified on clinical and genetic subgroups

Treatment:
Goals: Reduce (1) Symptoms (2) Thrombo-hemorrhagic Complications -- DOES NOT prevent dz transformation



*Cytoreduction agents include Hydroxyurea (HU), Interferon (Pegasys), and Anagrelide. The latter is an effective cytoreductive agent, but has a worse side-effect profile (cardiac toxicity, post-ET myelofibrosis) and does not lower the WBC. Lowering the WBC may be more important for thrombosis prevention than platelet normalization (**Eur J Haematol 2016;97:511**).
**Monitoring response every 3-6 mo. includes assessing for dz progression, determining symptom burden (MPN-SAF), and also evaluating for symptoms that would prompt starting or changing cytoreduction: (1) New thrombosis, acquired vWD, and/or dz-related major bleeding, (2) Splenomegaly, (3) Thrombocytosis, (4) Dz-related symptoms (i.e. pruritis, night sweats, fatigue), (3) Vasomotor/microvascular disturbances not resolved w/ ASA 81.

Polycythemia Vera (PV)

Epidemiology:

- Incidence: Estimated to be 1.9 per 100,000 (Am J Hematol 1994;47:89).
- Median age of Dx: 60 yrs. 25% of cases < 50 yrs, 10% < 40 yrs.
- Rare families w/ multiple cases of MPNs have been described, suggesting a possible underlying autosomal dominant mutation

Natural History:

- Often discovered incidentally or in the setting of a blood clot, particularly in unusual locations (such as abdominal vessels). RBC, WBC, and Plts may all be ↑.
- Physical exam may show conjunctival injection, plethora, splenomegaly, thrombotic complications.
- Labs findings include Hgb > 16 (women) and 16.5 (men), WBC > 10k, Plt > 450k, elevated LDH, smear w/ excess normocytic RBCs, thrombocytosis, leukocytosis.

Symptoms and Complications:

	Symptom	Mechanism/Further Thoughts
Aquagenic pruritis	Pruritus after a warm bath/shower, typically w/in 10 min. of water contact (Note: pruritis can occur anytime unrelated to shower/heat)	Possibly due to platelet aggregation → prostaglandin release v. mast cells releasing histamine
Hyperviscosity	HA, GI upset, transient vision changes, CVA, MI, DVT, atypical thrombi location (Budd Chiari, Splanchnic veins)	If patient has splanchnic vein thrombosis w/o other risk factors, think JAK2 mutation even if CBC normal
Bleeding	Superficial or mucosal bleeding, esp Plt > 1000k	↑ platelet binding of vWF multimers, leading to depletion
Erythromelalgia	Dysesthesias in hands/feet (burning, swelling, erythema). Seen in ET as well.	Microvascular thrombotic events, esp Plt > 400k
Gout	Monoarticular arthropathy	↑ cell prolif/turnover

Pathophysiology:

- Genetic mutations in a hematopoietic progenitor cell -> ↑ clonal expansion and downstream EPO-independent RBC proliferation. There are variable increases in platelets and myeloid cells.
- Essentially all PV patients have JAK2 mutations (95-97% w/ V617F mutation in exon 14, the remaining have exon 12 mutations). Small percentage have other mutations (LNK).
- While nearly all PV patients share a JAK2 mutation, their prognosis is heterogeneous; other mutated genes drive this heterogeneity, and studies are investigating which are clinically significant genes.

Diagnosis:

Per 2016 WHO Guidelines: need all three major WHO criteria, or the first two major criteria and the minor criterion

Major	Hgb/Hct > 16.5/49.0 (M) or > 16.0/48.0 (F)
	BM bx showing trilineage proliferation
	JAK2 V617F or JAK2 exon 12 mutation
Minor	Subnormal EPO level

Workup:

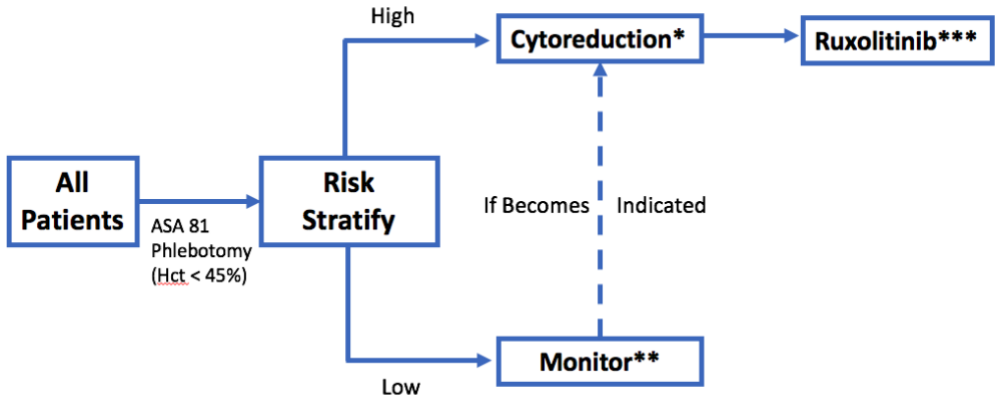
1. Repeat CBC w/ differential
2. Peripheral blood smear: should see excess of normocytic, normochromic RBCs (important to assess for leukoerythroblastosis which may be more suggestive of underlying fibrosis).
3. EPO level (repeat if 1st is normal)
4. Peripheral blood screening for JAK2 V617F (send JAK2 exon 12 screening if V617F negative)
5. BM bx

Prognosis:

- Outcomes worse for: 1) advanced age, 2) leukocytosis, 3) h/o DVT, and 4) abnl karyotype (Leukemia 2013;27:1874).
- Pruritis is a/w ↑ survival (unknown why).
- Survival is 6-18 mo. if untreated, but >13 yrs if treated.
- Causes of death: CV complications, thrombosis, transformation into AML (7% in 20 yrs) or myelofibrosis (12-20%)
- MPN Personalized Risk Calculator: for predicting overall survival, event-free survival, risk of progression to AML or MF; applies to all MPNs; risk stratified on clinical and genetic subgroups (NEJM 2018;379:1416).

Treatment:

Goals: Reducing (1) Symptoms and (2) Complications. From the PCV Group (PVSG) (Semin Hematol 1986;23:132)



*Cytoreduction agents include Hydroxyurea (HU) and Interferon (Pegasys)
**Monitoring response every 3-6 mo. includes assessing for dz progression, determining symptom burden (MPN-SAF), and also evaluating for reasons that would prompt starting or changing cytoreduction: (1) New thrombosis, acquired vWD, and/or dz-related major bleeding, (2) Intolerance/resistance to hydroxyurea or interferon, (3) Frequent/persistent need for phlebotomy w/ poor tolerance to them (4) Splenomegaly, (5) Thrombocytosis, (6) Leukocytosis (7) Dz-related symptoms (eg pruritis, night sweats, fatigue).
***Ruxolitinib is a JAK 1/2 inhibitor and FDA approved for those w/ inadequate response or intolerance to cytoreductive agents.

Myelofibrosis

- MF is the least frequent MPN w/ estimated prevalence of ~13,000. Median age of dx: 65 y/o
- Can be primary (PMF) or secondary (arising from PV or ET).

Pathophysiology:

- Myeloproliferative neoplasm w/ stem-cell derived clonal myeloproliferation and can evolve into AML.
- Mutations identified in PMF include JAK2, CALR, MPL (~90% of cases). Other mutations occur in majority of patients and help inform prognosis.
- MF w/o one of the 3 primary driver mutations - "triple negative MF" - carries a worse prognosis
- Bone marrow fibrosis leads to extramedullary hematopoiesis, commonly in spleen, liver, lymph nodes; more rarely also in vertebral column, lungs, retroperitoneum.

Natural History:

- Symptoms/history: severe fatigue, abdominal fullness from splenomegaly, "B symptoms" (fevers, night sweats, weight loss); transfusion requirements, thrombotic/hemorrhagic events
- Exam: massive splenomegaly (often below iliac crest), hepatomegaly
- Labs: anemia, high or low platelets and WBCs; left shift in WBC common (often w/ fluctuating blast count), smear shows leukoerythroblastosis (nucleated RBC, tear drops, and immature white cells)

Workup (NCCN; MPN, v.3.2019):

- Labs: CBC, peripheral smear, CMP including uric acid, LDH, LFTs, serum EPO level, PT/PTT/INR, vWF panel (if elevated platelets), and iron studies.
  - IF leukocytosis and/or thrombocytosis + basophilia → RT-PCR for BCR-ABL1 to exclude CML.
- Molecular Testing: JAK2 V617F mutation, if negative, MPL and CALR molecular testing
- Bone marrow bx: Characteristic finding is megakaryocyte proliferation and atypia + reticulin and/or collagen fibrosis. May identify prefibrotic PMF (morphology but only 1+ fibrosis), which resembles ET clinically but has worse outcomes than ET. Send for cytogenetic and molecular testing (i.e. Heme SnapShot panel)
- HLA testing possible allogeneic HCT candidates.

Diagnosis (Blood 2016;127:2391):

Per 2016 WHO Guidelines: need all three major WHO criteria, and at least one minor criterion

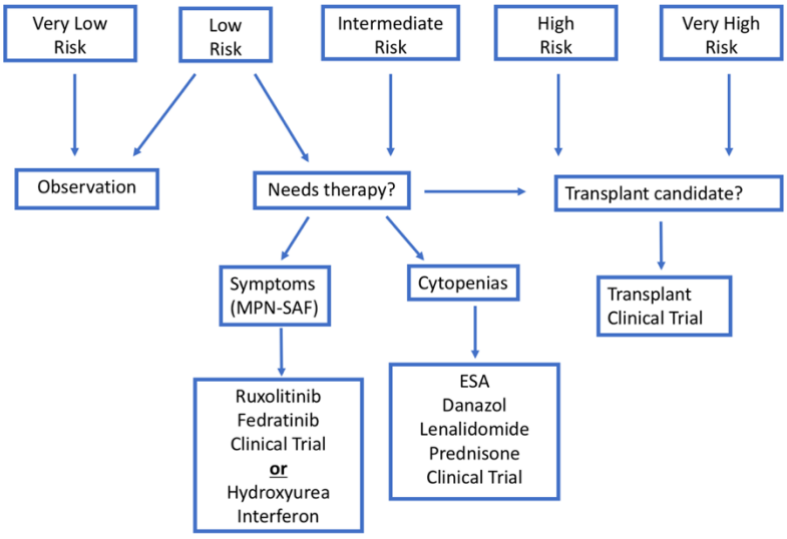
Major	Megakaryocytic proliferation and atypia w/either reticulin and/or collagen fibrosis grades 2 or 3
	Not meeting criteria for: ET, PV, CML, MDS, other myeloid neoplasms
	JAK2, CALR, MPL mutations OR presences of another clonal marker or absence of reactive myelofibrosis
Minor	Anemia
	WBC > 11k
	Palpable splenomegaly
	LDH above ULN
	Leukoerythroblastosis

Prognosis:

- Median life expectancy of PMF is 6 yrs, <6mos after AML transformation
- Prognostic factors: Age (>65), anemia (<10), leukocytosis (>25k), circulating blasts (>1%), constitutional symptoms, karyotype (favorable v. unfavorable), transfusion requirement, thrombocytopenia (<100k).
- DIPSS-plus score: Most commonly used. Separates pts into four risk groups (low, intermed. risk-1, intermed. risk-2, high risk) using the above factors
- MIPSS70+ score now increasingly used takes into account genetic mutations
- MPN Personalized Risk Calculator: for predicting overall survival, event-free survival, risk of progression to AML or MF; applies to all MPNs; risk stratified on clinical and genetic subgroups (**NEJM 2018;379:1416**)
- CALR mutation a/w better survival than JAK2 V617F or MPL W515 mutation (**NCCN; MPN, v.3.2019**)

Treatment (PMF) (NCCN; MPN, v.3.2019):

- Goal is to alleviate symptoms, reduce risk of leukemic transformation, and improve survival.
- Symptomatic tx is guided the MPN-SAF TSS (MPN Symptom Assessment Form Total Symptom score), which measures symptom burden and helps gauge response to tx.



Adapted from Clinical Resource provided by Dr. Gabriela Hobbs

Treatment Notes:
-Ruxolitinib is a JAK1/2 inhibitor. Trials have shown significant benefit in reduction of splenic size and constitutional symptoms, but have not shown significant improvement in cytopenias. Longterm follow up of Ruxolitinib studies demonstrate a survival advantage, however, the studies were not initially designed to test this.
-Fedratinib is a JAK2 inhibitor that is approved for tx of MF, either as initial tx (instead of Ruxolitinib) or second-line if no response w/ Ruxolitinib
-Allogeneic HCT is the only potentially curative tx w/ long-term remissions.

Anemia treatment:

- Replete iron, B12, folate
- IF EPO level < 500
    - Add Darbepoietin alfa or Epoietin alfra If EPO level < 500
- IF EPO level > 500
    - Consider Danazol (testosterone derivative) OR
    - Immunomodulatory agents (lenalidomide, thalidomide) +/- prednisone

Supportive care is critical part of management and includes managing cardiovascular risk factors, transfusion support if needed (leukocyte-reduced products recommended in transplant candidates), antifibrinolytic agents for refractory bleeding, iron chelation for certain patients, growth factor support for recurrent infections w/ neutropenia, appropriate vaccinations, and consideration of cytoreductive therapy for hyperproliferative manifestations.

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Overview

Hematopoietic stem cell transplantation (HSCT) refers to the infusion of hematopoietic stem cells (HSCs) from any source (bone marrow, peripheral blood, umbilical cord) or donor (autologous, allogeneic) to reconstitute blood production.

- HSCT was performed for the first time in the late 1950s to rescue blood production in patients who had received high doses of chemotherapy or radiation for various types of malignancies
- HSCT is broadly classified as ***autologous (own patient's stem cells)*** or ***allogeneic (someone else's stem cells)***
- HSCT is currently used primarily for the treatment of hematologic malignancies, and less commonly for solid cancers or benign hematopoietic and immunological disorders
- Over 22,000 transplants are performed annually in the US, where the most common indications are multiple myeloma (MM), non-Hodgkin lymphoma (NHL) and AML

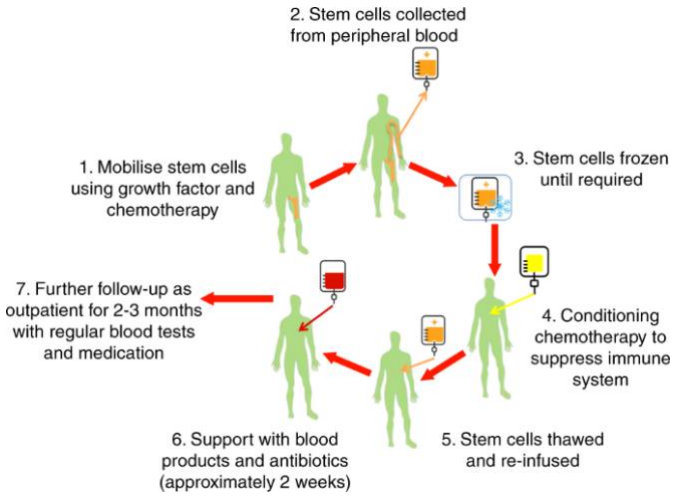


Image courtesy ***BMT 2019;54:933***

Most common indications for HSCT:

Autologous	Allogeneic
1. MM	1. AML
2. NHL	2. MDS/MPN
3. HL	3. ALL
4. Other cancers	4. NHL
	5. CML

In contrast to ***allogeneic HSCT***, in which the transplanted hematopoietic cells are largely intended to produce ***graft-versus-tumor*** activity, the primary goal of ***autologous HSCT*** is to ***reconstitute ("rescue") hematopoiesis*** after a myeloablative chemotherapy regimen. There is growing evidence that autologous HSCT may also produce a graft-versus-tumor effect via CD8+ T cells (**JCI 2019;129:48**). Autologous HSCT is more commonly used for MM, NHL (e.g. DLBCL) and HL, either as post-induction consolidation to deepen response or for treating relapsed disease.

- Disease-specific indications include:
  - MM: Consolidation or upon relapse (generally not "curative," although some remissions last >5 years)
  - AL amyloidosis: Consolidation (to eradicate small AL clone)
  - NHL: Consolidation or upon relapse (if demonstrated response s/p salvage chemotherapy regimen)
  - HL: Upon relapse
  - Selected solid tumors (e.g. relapsed testicular cancer)
  - Metastatic neuroblastoma (primarily pediatric patients)
  - Autoimmune diseases (e.g. multiple sclerosis)

Mobilization and collection of HSCs

For autologous transplants (auto-transplants), stem cells are almost always obtained from peripheral blood (PBSCs: peripheral blood stem cells). HSCs are mobilized and collected a few weeks prior to the transplant preparative regimen. Strategies for HSC mobilization include: 1) GSCF alone, 2) GCSF + plerixafor, 3) GCSF + chemotherapy, and 4) GCSF + plerixafor + chemotherapy. Plerixafor (a CXCR4 inhibitor), which works by blocking the interaction between HSCs and bone marrow stromal cells, is generally added when GCSF is ineffective.

Conditioning (or preparative) regimen *(note: times vary for the preparative regimen)*

The timing and schedule of consolidation depends on the specific regimen used. In auto-transplants, the only goal of the conditioning regimen is to eradicate the malignant cells (in allo-transplants, it also provides immunosuppression to prevent graft failure). Commonly used regimens include:

- **BEAM:** Combines carmustine (BCNU), etoposide, Ara-C and melphalan. This is the most used regimen for patients with HL and NHL, as well as subset of patients with extramedullary MM

- **CBV:** Combines cyclophosphamide, BCNU and etoposide (VP-16). Commonly used in the preparative regimen for patients with HL
- **Melphalan:** Standard regimen for auto-transplants in MM and AL amyloidosis. 200 mg/m2 (MEL200) is traditional dose if normal renal function
- **TBC:** Combines thiotepa, busulfan and cyclophosphamide. More commonly used for primary CNS lymphoma and for NHL involving the CNS

Infusion of HSCs (Day 0)
Autologous products are thawed at the bedside and infused intravenously (takes around 10-15 minutes per bag). Minor toxicities such as fever, nausea, vomiting and headaches are relatively common.

Engraftment (Days 7-10)
Defined as attainment of an ANC > 500 for three consecutive days. The use of **GCSF** (Neupogen or Granix) shortens the time to engraftment without demonstrated effect on mortality (Blood 2006;107:1712).

Complications
Autologous transplants are a/w fewer complications compared to allogeneic transplants. GVHD is very rare (since the transplanted cells are "self"), engraftment happens sooner and severe infections are less common. The treatment-related mortality of autologous HSCT at one year is generally <5%. Different scoring systems have been developed to predict the risk of treatment-related mortality, such as the **Pre-transplantation Assessment of Mortality (PAM)** and the **HSCT Comorbidity Index (HSCT-CI)**. However, these systems have been studied mainly in the allogeneic setting.

The following **short-term complications** can be seen following either autologous or allogeneic HSCTs:

- **Mucositis:** Most patients who undergo HSCT develop significant mucositis. Patients undergoing autologous HSCT generally recover faster and usually do not require TPN. **Palifermin** (recombinant keratinocyte growth factor) may reduce the duration and severity of mucositis.
- **Bleeding:** 5-10% of patients undergoing HSCT experience a life-threatening hemorrhagic event, with GI, GU and pulmonary bleeding being the most common sites.
- **Sinusoidal obstruction syndrome (SOS):** Formerly known as hepatic veno-occlusive disease (VOD), it is characterized by weight gain, hepatomegaly, ascites and jaundice. Dx: RUQUS w/ Doppler to evaluate for reversal of flow. Ppx: **ursodiol** is generally started one day before the first conditioning dose, continuing until approximately day +30. Shown to decrease incidence of SOS, may improve OS at one year (Blood 2002;100:1977). **Defibrotide** is often used for severe SOS, but limited data and high cost.
- **Diffuse alveolar hemorrhage (DAH):** ~2% of autologous HSCT recipients. Presents in first 2 weeks post-HSCT with tachypnea, dyspnea and hypoxia. Hemoptysis is present in a minority of patients. Imaging shows diffuse ground glass or consolidative opacities. Alveolar hemorrhage is confirmed by bronchoscopy, which shows progressively more hemorrhagic BAL aliquots. Treatment consists of pulse **steroids**, but prognosis is generally poor.
- **Engraftment syndrome:** Presents within 96 hours of engraftment w/ non-infectious fever, an erythrodermatous/maculopapular rash, hypoxemia with diffuse lung opacities on CXR, evidence of capillary leak (edema, ascites, hypoalbuminemia), and diarrhea. Tx: includes **empiric Abx** and **systemic steroids** (for patients with high fever of a non-infectious etiology or respiratory involvement).

Because ***GVHD*** usually ***does not develop*** (rare GVHD-like syndrome occurs in ~0.5% of autologous transplants, (BMT 2020;55:1879)), ***long-term immunosuppression is not required*** in ***autologous HSCTs***, and late complications are less common compared to allogeneic HSCTs.

Late complications seen in autologous and allogeneic HSCTs include:

- **Cardiovascular disease:** risk of CAD, CHF, arrhythmias is ↑ following transplant. CV-related death among HSCT survivors is significantly higher compared to the general population
- **2º malignancies:** recipients of autologous and allogeneic HSCTs have ↑ risk of second solid malignancies, MDS and post-transplant lymphoproliferative disorder (PTLD)
- **Fertility problems:** Sterility is common following HSCTs, although the risk varies depending on the consolidating regimen used

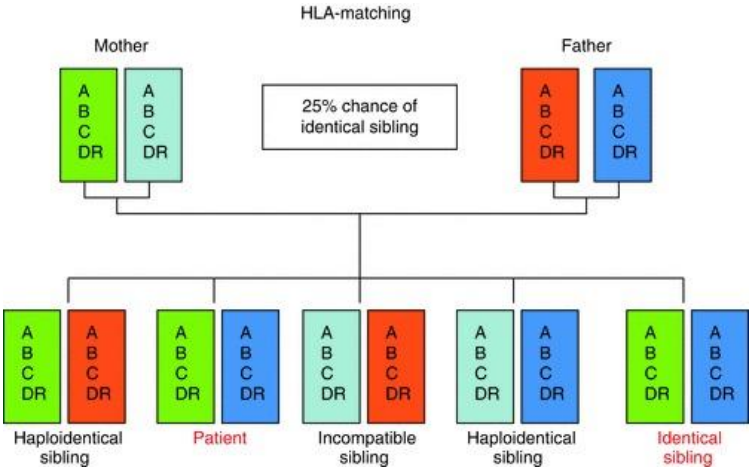
Overview and Indications

Allogeneic transplants are typically used for patients whose condition would otherwise be considered incurable. In acute leukemias, allo-HCST is generally offered to patients in remission if it offers results superior to those achieved w/ non-transplant options. In chronic conditions (such as chronic leukemias and indolent lymphomas), allo-HSCT is generally reserved for patients who have failed targeted therapies, conventional chemotherapy, or who have evidence of aggressive transformation. Specific-disease indications include:

- AML and ALL: Used for consolidation therapy in first or subsequent remission or in patients w/ high-risk disease who have a low chance of cure w/ chemotherapy alone
- CML: Tx of accelerated phase or blast crisis or patients resistant or intolerant to TKIs
- NHL: Tx of relapsed disease (often after auto-transplant) or for aggressive disease for which an auto-HSCT is not likely to be effective
- MPN/MDS: higher risk disease w/ high risk of mortality or leukemic transformation
- Nonmalignant disorders: Tx of bone marrow failure syndromes/aplastic anemia, sickle cell anemia, beta-thalassemia major, paroxysmal nocturnal hemoglobinuria

Principles of HLA matching

Because HLA genes are located in close proximity on chromosome 6, they usually are inherited together as a set. Therefore, for any given mother and father, there are four possible sets of HLA antigens in their children. A 6/6 full-match donor refers to one that matches at **6 alleles** (**HLA-A**, **HLA-B** and **HLA-DRB1** from each parent). A **haploidentical** donor refers to one who matches at one haplotype (**3/6 HLA genes**). A sibling has a 25% chance of being an identical donor, and a 50% chance of being haploidentical. Finally, parents and children are always haploidentical to each other. Typing of **10 HLA alleles** (**HLA-A**, **HLA-B**, **HLA-C**, **HLA-DRB1**, and **HLA-DQB1**) is the standard at many centers. In this case, a full-match refers to a 10/10 match.



Soiffer RJ, editor. Haematopoietic stem cell transplantation. 2nd ed: Humana Press; 2008

Recipient-donor immune interactions

- **Graft-versus-tumor (GVT):** a desirable interaction in which the donor immune system recognizes the recipient's cancer cells as foreign and seeks to destroy these cells. Graft-versus leukemia (GVL) or graft-versus lymphoma (GVL) are specific terms for GVT in the setting of hematologic malignancies.
- **Graft-versus-host disease (GVHD):** common complication of allo-HSCT in which the immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (the host) as foreign, thereby causing an inappropriate immune reaction in the transplant recipient.

Types of Allogeneic Transplants

Allogeneic transplants are classified based on the donor as matched related donor **(MRD)**, matched unrelated donor **(MUD)** and alternative donors, such as haploidentical or mismatched unrelated.

- **Matched related donor (MRD):** HLA 10/10 match. When available, MRD is preferred due to improved outcomes following transplant (less GVHD) and the speed of the search. MRD transplants are a/w less morbidity from GVHD, but OS is similar to MUD (**Blood 2010;116:1839**).

- **Matched unrelated donor (MUD):** HLA 8-9/10 match. When an MRD is not available, the search should center on a matched unrelated donor (MUD). MUDs are identified via the National Marrow Donor Program. The time from search to donor availability is usually weeks to several months. The likelihood of finding a match varies by race, from 75% for whites to 16% for blacks. MUD transplants are a/w increased morbidity from GVHD, but transplant-related mortality and 5-year survival are comparable to MRD transplants.
- **Alternative donors:**
  - Mismatched unrelated donor (MMUD): Generally mismatched at one HLA antigen (9/10 match). Are a/w a higher risk of GVHD and graft failure.
  - Haploidentical: Generally mismatched at 3/6 or 5/10 loci (HLA-A, -B and -DRB1). Haplo-transplants are a/w a higher risk of rejection, GVHD and transplant-related mortality. However, the increased GVT effect (via NK cells) may decrease the risk of relapse in high-risk patients (**Blood 2013;121:849**). Newer regimens of GVHD ppx (see below), in particular post-transplant cyclophosphamide (PTCy), have permitted their use w/ OS rates similar to those of MUD (**JAMA Oncol 2019;5:1739**) and MRD (**JCO 2013;31:1310**) transplants. Parents and children are always haploidentical, as are 50% of siblings.
  - Umbilical cord blood (UCB) transplant: Grafts are obtained from cord blood banks. Slower engraftment of cord stem cells leads to higher risk of graft failure and transplant-related complications. However, the risk of GVHD is lower, allowing for HLA mismatches (4/6 or 5/6 HLA match) (**NEJM 2004;351:2276**), which can facilitate decreased time to transplant.
  - Identical twin (syngeneic) transplants: are similar to auto-transplants from a biological and clinical standpoint. They do not require immunosuppression and do not develop GVHD, but have a higher risk of relapse due to the absence of GVT effect (**Ann Intern Med 1994;120:646**).

Stem Cell Source

- Bone marrow (BM): Most traditional and most studied source of HSCs. Usually obtained in the OR through multiple aspirations (>100) from the iliac crest, for a total volume of 1-1.5 L of bone marrow. The procedure takes about 1 hour and serious complications are rare.
- Peripheral blood (PB): Overall survival (OS) is the same between those receiving PB and BM transplants (**Cochrane 2014;4:CD010189**). However, engraftment occurs faster w/ PB compared to BM or UCB, but rates of GVHD are higher. Disease-free survival in patients w/ aggressive disease may be better w/ PB (at least after MRD HSCT), probably due to increased GVT effect.
- Umbilical cord blood (UCB): Stem cells are obtained from cord blood banks. Limitations of UCB include unavailability of the donor for additional donations and a limited number of HSCs present in the graft, leading to delayed reconstitution, longer time to neutrophil engraftment and increased risk of graft failure. The use of double cord transplants reduces the risk of graft failure (even though in general only one cord engrafts), but increases the risk of GVHD (**NEJM 2014;371:1685**).

Studies have shown **similar OS following MRD, MUD and haplo-transplants**. MRDs are a/w the least risk of GVHD, but the risk of relapse may be higher due to decreased GVT effect. On the contrary, the risk of GVHD is higher in mismatched transplants, but the GVT effect may be stronger, decreasing the risk of relapse (**Blood 2003;102:1541**). Additionally, improved prophylaxis regimens against GVHD such as cyclophosphamide (discussed below) can markedly reduce this risk in mismatched donors (**JCO 2013;31:1310**).

Because the risk of GVHD and relapse vary by donor source and disease, the preferred type of transplant varies for each patient. When a MRD is not available, the search for a donor must consider the risks of postponing the transplant while performing an extensive search. If the risk of relapse is high, proceeding w/ an alternative donor (haploidentical, UCB transplant or unrelated mismatched) may be preferable. Other preferred characteristics of donors include younger age, men or nulliparous women (as prior pregnancy increases the risk of a donor harboring alloreactive memory lymphocytes), matched for CMV status, and matched blood type.

Preparative (or Conditioning) Regimens

The goal of the conditioning regimen is to eradicate the underlying disease, and to provide immunosuppression to prevent graft failure. Preparative regimens can be divided as follows:

- Myeloablative: These regimens cause irreversible BM aplasia, resulting in profound, fatal pancytopenia, unless hematopoiesis is restored w/ new HSCs. They are a/w the highest risk of infections, lung and liver toxicities and more transfusions, but ↓risk of relapse (**JCO 2009;27:4570**). Preferred for younger, fit patients. Commonly used regimens include cyclophosphamide + total body irradiation (Cy/TBI), busulfan + cyclophosphamide (Bu/Cy), and fludarabine + busulfan (Flu/Bu).

- Reduced-intensity conditioning (RIC): Toxicities are significantly lower than w/ myeloablative regimens, but higher than w/ non-myeloablative. They cause severe cytopenias that may result in significant morbidity and mortality. Examples include Flu/Melphalan (Flu/Mel), Flu/Cy, and reduced intensity Flu/Bu.
- Non-myeloablative: A/w minimal cytopenias (but profound lymphopenia). Relies less on the regimen and more on the GVT effect to eradicate malignant cells. Regimens include Flu/TBI, low dose TBI, and total lymphoid irradiation (TLI) + ATG (anti-thymocyte globulin = T-cell-depleting antibodies). Non-myeloablative and reduced-intensity HSCTs are referred to as "mini-transplants".

Side effects of conditioning All regimens except ATG: marrow toxicity, N/V, diarrhea, mucositis, alopecia, rash, infertility	
TBI	Severe mucositis, sinusoidal obstruction syndrome (SOS, see below), parotitis, sicca syndrome
Cyclophosphamide	Hemorrhagic cystitis, myopericarditis, SIADH, SOS
Busulfan	ILD, seizures, SOS
Fludarabine	Peripheral edema, angina, visual changes, rash
Carmustine	Lung fibrosis, seizures, encephalopathy, SOS
Melphalan	Mucositis and enteritis
ATG	Serum sickness reaction (fevers, chills, arthralgias), rash, thrombocytopenia

Myeloablative regimens are used for autologous HSCTs, and in the allogeneic setting for patients w/ good performance status and w/o significant co-morbidities, who are usually < 60 years old, and who are not in complete remission or have high-risk disease. The choice of preparative regimen depends on:

- Disease type: Myeloablative regimens are preferred for malignancies in which the goal is complete eradication of the malignant cells. Less intensive regimens are used in benign conditions, in which the goal is immunosuppression to prevent graft failure
- Disease status: Myeloablative regimens are preferred for malignancies that are not in complete remission
- Health of recipient: Myeloablative regimens are reserved for patients w/ good performance status
- Risk of rejection: Patients who are at high risk of rejection may benefit from the addition of ATG to deplete host T cells

Blood Product Support and Engraftment

Time to engraftment	
Auto-PB	+8 to +11
Allo-PB	+12 to +15
Allo-BM	+14 to +17
UCB	+24 to +28

Cell counts reach a nadir about 3-6 days after completion of the preparative regimen and patients become transfusion-dependent for 1 to 3 weeks. For transfusion of RBCs, a threshold of Hb 7-8 is commonly used. For platelet transfusions, the recommended threshold is 10,000, or higher in certain situations (bleeding, invasive procedure, rapidly declining plt count). Engraftment occurs around day 10-21, depending on the source of HSCs and preparative regimen. Absence of engraftment (graft failure) is usually the result of rejection by the recipient's T cells. Risk factors include: 1) HLA-mismatch, 2) multiple prior transfusions, 3) mini-regimens, and 4) T-cell depletion of donor marrow.

- CMV-status: CMV-seronegative patients w/ a CMV-seronegative donor should receive seronegative products, as available (CMV "safe" blood products via leukoreduction are an acceptable alternative). In addition, blood products must be irradiated (to prevent transfusion-associated GVHD "ta-GVHD") and leukocyte-reduced (to prevent HLA-alloimmunization and CMV transmission and to reduce the risk of febrile nonhemolytic transfusion reactions).
- Chimerism: After engraftment, hematopoiesis can derive entirely from the donor (complete or 100% chimerism), from the donor and recipient (mixed chimerism), or only from the recipient (graft failure). Chimerism studies help assess engraftment, graft failure and early relapse.

Complications

GVHD: GVHD is a significant cause of morbidity and mortality among allo-HSCT recipients. GVHD is classified as acute (generally occurring w/in 3 months, or after discontinuation of immunosuppression) and chronic (generally after three months, but can develop at any time). Acute GVHD occurs in 30-40% of MRD transplants. Risk factors include HLA mismatch, use of PB, donor and recipient gender disparity, CMV status of donor/host, donor EBV seropositivity, older age of donor/recipient, myeloablative regimen and multiparous woman as donor. Acute GVHD typically manifests in the skin, intestine and liver. Chronic GVHD, on the other hand, occurs in 20-50% of MRD transplants; it resembles a collagen vascular disease, affecting the skin, eyes, mouth, liver, lungs, esophagus, and less frequently, serosal surfaces and genitalia. Risk factors are similar as those for acute GVHD.

Clinical staging of acute GVHD

Stage	Skin (rash)	Liver (Tbili)	Gut (diarrhea)
I	<25% of body surface	2-3 mg/dL	500-1000cc
II	25-50% of surface	3-6 mg/dL	1000-1500cc
III	Generalized erythroderma	6-15 mg/dL	>1500cc
IV	Bullae, Desquamation	>15 mg/dL	>2000 cc, pain or ileus

GVHD prophylaxis: A choice among regimens must take into consideration the underlying disease, the degree of HLA disparity, the conditioning regimen, and patient characteristics. Common regimens:

- **MTX + tacrolimus:** Most common regimen in the US. Side effects include hypomagnesemia, mucositis, AKI, neurotoxicity (including PRES) and thrombotic microangiopathy. Leucovorin can be used to counteract the side effects from impaired clearance of MTX.
- **Sirolimus + tacrolimus:** Similar rates of GVHD and OS to MTX + tacrolimus. A/w less mucositis, but higher risk of LFTs abnormalities and sinusoidal obstruction syndrome (SOS).
- **Post-transplant cyclophosphamide (PTCy):** Causes more prolonged cytopenias (HSCs are selectively resistant, so engraftment is not significantly affected). Becoming the standard of care for haplo-and MMUD transplants, and being actively investigated in clinical trials for MRD/MUD transplants.
- **T cell depletion:** accomplished in-vivo employing **ATG** (antithymocyte globulins), or ex-vivo via CD34 selection or using anti-T-cell monoclonal antibodies. Used in MUD and haplo-transplants, to decrease the risk of severe GVHD; a/w higher risk of relapse (less GVT effect) and graft failure (**Lancet 1987;2:175**). Often used in transplants for benign heme conditions.
- If there are no signs of GVHD, immunosuppression can be tapered after 90 days and discontinued by 6-8 mo post-transplant. A theoretical concern of GVHD ppx is that it also decreases the GVT effect, increasing the risk of relapse. Relapse rates are lower when GVHD develops, and greater if T-cell depleted allografts are used. As such, ppx must be balanced to reduce the risk of severe GVHD w/o compromising the GVT effect.

Other non-infectious complications

Early complications (pre-engraftment): Usually a consequence of the preparative or GVHD prophylaxis regimens. (See also "Complications" in preceeding Autologous HCT section.)

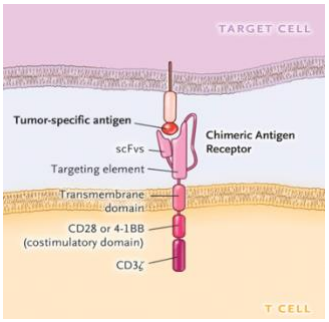
- Mucositis: More severe w/ myeloablative regimens, and when MTX is used for GVHD prophylaxis. It often involves the oropharyngeal and intestinal mucosa, compromising nutrition, and in some cases, requiring TPN.
- Sinusoidal obstruction syndrome (SOS) (see details in Autologous HCT section)
- Thrombotic microangiopathy (TMA): Characterized by microangiopathic hemolytic anemia, thrombocytopenia and AKI. It is caused by platelet-rich thrombi in the microvasculature. Often a/w calcineurin inhibitors, and usually responds to their discontinuation.
- Engraftment syndrome: Similar to that seen after auto-HSCT, it may portend a higher risk of early acute GVHD
- Idiopathic pneumonia syndrome: Develops in 5% of patients, around 30-90 days post-transplant. Presents w/ dyspnea, dry cough, hypoxia and diffuse interstitial opacities. It is more common when TBI is used. Mortality is 50-70%. Tx involves high-dose glucocorticoids.
- DAH: may be a consequence of infection, acute GVHD, or diffuse alveolar damage. Patients typically have patchy or diffuse opacities w/ air bronchograms on HRCT. The diagnosis is typically made by BAL. Tx depends on the underlying cause of DAH.
- Posterior reversible encephalopathy syndrome (PRES): More commonly seen when calcineurin inhibitors are used for GVHD prophylaxis. Presents w/ headaches, AMS, visual changes and seizures.
- Neuro-psychiatric: ~50% of patients experience delirium after HCT, especially during the first 30 days. Delirium may be a/w complications (eg, aspiration, falls), decreased performance status, and longer hospital stays.

Late complications: Day +30, usually manifest beyond one year after transplant, median day +70-90 (**NEJM 2018;378:549**). Can be a consequence of either chronic GVHD or long-term effects of the preparative regimens

- Bronchiolitis obliterans: Characterized by dyspnea, cough and CT appearance of air trapping. Highly a/w chronic GVHD, which leads to collagen deposits around bronchioles. Tx is largely unsatisfactory but usually consists of systemic immunosuppression and inhaled corticosteroids
- Cardiovascular disease: As w/ autologous transplants, the risk of CAD, CHF, arrhythmias and overall CV death is increased following transplant
- Liver disease: Chronic GVHD, medications, reactivation of viral hepatitis, iron overload and secondary hemochromatosis which has been reported in 25-60% of pts after allo-HCT

- Renal disease: Thrombotic microangiography, drug toxicity (eg, calcineurin inhibitors), nephrotic syndrome, and membranous glomerulopathy
- Endocrine disease: Diabetes (from steroids and calcineurin inhibitors), hypothyroidism (esp after TBI regimens), osteopenia/osteoporosis (due to impaired calcium and vitamin D homeostasis, osteoblast and osteoclast dysfunction, hypogonadism, and post-transplant steroids)
- Other complications: Myeloablative regimens almost always cause permanent sterility. Patients are at increased risk of second malignancies, including MDS/AML and PTLD, as well as skin cancers. Patients have a 30% lower life expectancy compared to the general population. The leading causes of excess deaths following allogeneic HCT, in order, are relapse, GVHD, infection, CV events, and secondary malignancies

Chimeric antigen receptors (CARs) = engineered fusion proteins
- *extracellular domain* = antigen-recognition region of a B-cell receptor → binds specifically to antigen on cancer cells (e.g. CD19 on a B cell)
- *intracellular domain* = intracellular portion of T-cell receptor CD3ζ subunit + signaling domain of T-cell co-stimulatory receptors (e.g. CD28 or 4-1BB) → activates T cells when the receptor is engaged with its target (NEJM 2018; 379:64).



Indications:

Name	Target	FDA approved for
Kymriah (tisagenlecleucel)	CD19	Relapsed/refractory B-ALL age <25yo (**ELIANA trial**, NEJM 2018;378:439). In adults, relapsed B-cell ALL (NEJM 2018;378:449) and adult relapsed DLBCL (**JULIET trial**, NEJM 2019;380:45).
Yescarta (axicabtagene ciloleucel)	CD19	Adult patients with relapsed/refractory large B-cell lymphoma, including DLBCL, primary mediastinal large B-cell lymphoma and high-grade B-cell lymphoma (**ZUMA-1**, NEJM 2017;377:2531).
Tecartus (brexucabtagene autoleucel)	CD19	Relapsed/refractory mantle cell lymphoma (**ZUMA-2,** NEJM 2020;382:1331) and B-cell ALL (ZUMA-3, Lancet 2021;398:491)
Breyanzi (lisocabtagene maraleucel)	CD19	Relapsed refractory lymphoma (**TRANSCEND**, Lancet 2020;396:839)
Abecma (idecabtagene vicleucel)	BCMA	Relapsed/refractory multiple myeloma (**KarMMA**, NEJM 2021;384:705)
Carvykti (Ciltacabtagene autoleucel)	BCMA	Relapsed/refractory multiple myeloma (**CARTITUDE-1**, Lancet 2021;398:314)

Other targets under investigation: (phase I/II) with variable success, including: anti-IL13Rα2 and EGFRvIII in GBM (NEJM 2016;375:2561, Sci Transl Med 2017;9:399), CD22 in relapsed ALL naïve or resistant to CD19 CAR T (Nat Med 2018;241:20), antigens for solid cancers include CEA (GI cancers, breast cancer), mesothelin (ovarian cancer, GBM), Her2 (breast cancer, neuroblastoma), and others (EGFRvIII, Epcam, HER2, MUC1, etc.) (Front Immunol 2019;10:128), combination with checkpoint inhibitors (PD1) and CAR T (Cancer Cell 2019;36:471).

CAR T cell Therapy Workflow
T cell isolation and activation: The T cells are collected from the peripheral blood of the patient by leukapheresis. The population is activated with anti-CD3//CD28 beads or bound antibody, and additional activating cytokines such as IL-2, IL7 and IL-15. This allows for optimization of cellular proliferation and likelihood of viral transduction during the engineering stage. In some instances allogeneic CAR-T or CAR-NK products are being developed and utilized in newer trials.
Genetic engineering of CAR T cells: The DNA encoding the CAR construct is transferred ex-vivo into the patient's T cells employing a retrovirus or lentivirus, and the engineered T cells are expanded ex-vivo. Newer generations of genetic engineering (e.g. CRISPR) are now being used for both genetic knock-outs as well as targeted gene insertion (Nature 2017;543:113).
Lymphodepletion: The patient generally undergoes a lymphodepleting chemotherapy regimen with the goal of (1) decreasing the circulating lymphocyte count which can lead to a, (2) increase in homeostatic cytokines to optimize CAR-T expansion, while (3) modulating the tumor microenvironment ex. Reduction of Treg populations. ELIANA, ZUMA-1, JULIET trials used varying doses of cyclophosphamide/fludarabine. JULIET did allow for single agent bendamustine as lymphodepletion.
CAR T-cell infusion: Dose of CAR-T cells varies by protocol, optimal cell number, number of doses that provide maximal efficacy and minimal toxicity change for each protocol.

COMPLICATIONS:

Cytokine-release syndrome (CRS)

- Overview: most frequent serious side effect a/w CAR T-cell therapies, nearly all patients have some manifestations, up to one third have significant CRS. Widespread immune activation → elevated inflammatory cytokines (IL-6, IFN-g, TNF-a, IL-10) and activation of T cells, macrophages, endothelial cells.
- Risk factors: increased tumor burden (due to higher levels of T-cell activation), high dose of CAR T-cells, high baseline inflammatory markers, and robust CAR-T expansion

- Presentation: usually shortly after infusion (1-14d, median 2-3 d). Ranges from mild flu-like symptoms to high-grade fever (≥38ºC diagnostic req.), hypotension, hypoxia, SIRS, ARDS, DIC, hepatic, renal and HF bordering on macrophage activation syndrome
- Work-up: Dx is usually based on clinical presentation. r/o infection in all patients p/w sx suggestive of CRS and start on broad spectrum antibiotics. Patients will have cytopenias and should be treated as a neutropenic fever. ↑↑↑ levels of inflammatory cytokines (assays not available at most hospitals). CRP can increase by several logs; **trend CRP and ferritin levels** → identify patients at risk for severe CRS, or peak in individual patient. Dramatically **elevated IL-6** supports Dx.
- Dx: CBC w/ diff, Coags, BMP, LFTs, LDH, uric acid, ABG, inflammatory markers, microbiological testing, CXR, CRP and ferritin
- Tx: **Tocilizumab** (anti-IL-6R) 8 mg/kg (max dose 800 mg), or siltuximab (anti-IL6) **+/- corticosteroids** for moderate to severe CRS. **These agents should only be given after discussion with the covering attending.** Additional studies are underway examining alternative agents such as anakinra and JAK/STAT inhibitors, these agents may sometimes be used in refractory patients.
- Steroids are immunosuppressive and may dampen antitumor activity of CAR-T cells. One study showed that high dose steroids rapidly reversed CRS symptoms but ablated CAR T cells and were a/w recurrence of dz after initial response to CAR T therapy (**Sci Transl Med2014;6:224**). Although steroids have been shown in other instances not to impact CAR T expansion, aggressive and long-term use of steroids should be avoided given these mixed data. Empiric abx must be initiated until infection r/o

ASTCT CRS Consensus Grading

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temp ≥ 38ºC	Temp ≥ 38ºC	Temp ≥ 38ºC	Temp ≥ 38ºC
Hypotension	None	+ hypotension not requiring vasopressors	Requiring a vasopressor +/- vasopressin	Requiring multiple vasopressors (excluding vasopressin)
Hypoxia	None	And/or requiring low-flow NC	And/or Requiring high-flow NC, nonrebreather, Venturi mask	And/or Requiring positive pressure (CPAP, BiPAP, intubation/vent)

Neurotoxicity: ICANS (immune effector cell-associated neurotoxicity syndrome), previous term CAR T-cell-related encephalopathy syndrome (CRES)

- Definition: "Disorder characterized by a pathologic process involving the CNS following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells". *ASTCT definition*
- Pathophys: systemic inflammation and high levels of circulatory cytokines (IL6, IL1) results in endothelial cell activation and BBB disruption → causes inflammatory cascade in CNS → AMS +/- diffuse cerebral edema.
- CAR T-cell-associated neurotoxicity is thought to be related to CRS, although may occur independently of CRS. Mechanisms include endothelial activation, macrophage activation syndrome and increased BBB permeability. Recent data has suggested that the myeloid/monocyte compartment is primarily responsible for robust cytokine proliferation and excessive activation (MAS) a/w ICANS. As glial cells are monocyte derived they have the ability to respond to inflammatory cytokines similarly to peripheral.
- Presentation: Neuropsychiatric syndrome, may present with tremor, dysphagia, **altered level of consciousness**, delirium, **expressive aphasia**, encephalopathy, **impaired cognitive skills**, **motor weakness**, **seizures**, **cerebral edema**. Several deaths due to neurotoxicity have been reported in anti-CD19 CAR T-cell trials.
- Timing: 2-4-d after infusion. Duration 14-17d.
- Dx: Grading composite score of (1) **ICE score** (immune effector cell-associated encephalopathy assessment), (2) **depressed level of consciousness**, (3) **seizure**, (4) **motor findings**, (5) **elevated ICP/ cerebral edema**. **ASTCT Consensus Grading Lee et al. 2019**
  - **ICE score (total 10):** Orientation (year, month, city, hospital, 4 points), naming (name 3 objects, 3 points), following commands (1point), writing (1 point), attention (count backwards from 100, 1 point). ICE scores are calculated by nurses at least qshift.
  - Dx studies: MRI brain w/wo contrast (Brain MRI is often normal), EEG, +/- LP, fundoscopic exam, neuro consult.

- Tx: corticosteroids (e.g. dexamethasone 10 mg IV Q6H, methylprednisolone 1mg/kg/day), anakinra (IL1 inhibitor) or tociluzimab may be given
  - Steroid dosing is ideally set and reassessed every 12-24 hrs. Unlike GVHD, patients do not need a slow steroid taper and can usually stop steroids within 3-7 days of initiation. Complications from long-term steroid use include decreased efficacy, increased infectious complications, steroid myopathy, and adrenal insufficiency.
  - Start seizure ppx on day of infusion (levetiracetam 500-750 mg q12h for 30d)

ASTCT ICANS Consensus Grading for Adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score	7-9	3-6	0-2	0 (patient is not arousable, unable to perform ICE)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma
Seizure	N/A	N/A	Focal or generalized seizure that resolves rapidly; or non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Raised ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; Decerebrate or decorticate posturing; or Cranial nerve VI palsy; or Papilledema; or Cushing's triad

CAR-T-cell-related hemophagocytic lymphohistiocytosis (HLH) / macrophage activation syndrome (MAS)

- Pathophys: Hyperactivation of macrophages and cytotoxic T cell hyperactivation, proinflammatory cytokine production, lymphohistiocytic tissue infiltration, immune-mediated multiorgan failure. Develops in 1% of CAR T cell patients.
- Presentation: high fever; multiorgan dysfunction (↑LFTs, kidney failure ↑Cr, coagulopathy, lung, haemophagocytosis in BM or other organs), CNS disturbances
- Dx: similar to HLH, ↑↑↑ ferritin levels, ↑LDH, ↑ soluble CD25, and ↑ cytokines (IFNγ, IL-6), ↓ fibrinogen levels
- Tx: high mortality, treat aggressively. anti-IL-6 therapy and corticosteroids as per CRS algorithm. Can consider adding etoposide to Tx and intrathecal cytarabine for neurotoxicity.

Tumor lysis syndrome

- The pathophysiology, manifestations and Tx are the same as those with chemotherapy (*See Section 9.1: Cancer Emergencies*). It is important to differentiate TLS from CRS, and to treat for both if indicated.

On-target, off-tumor effects

- The majority of tumor antigens are also expressed in normal tissues, leading to off-tumor effects.
- B-cell aplasia is a common adverse event of anti-CD19 CAR T-cells, usually managed w/ gamma globulin replacement.
- Rapid respiratory failure has been reported in trials targeting ErbB2, due to the recognition of the antigen in normal lung tissue. Clinical trials aimed at minimizing these off-tumor effects are undergoing.

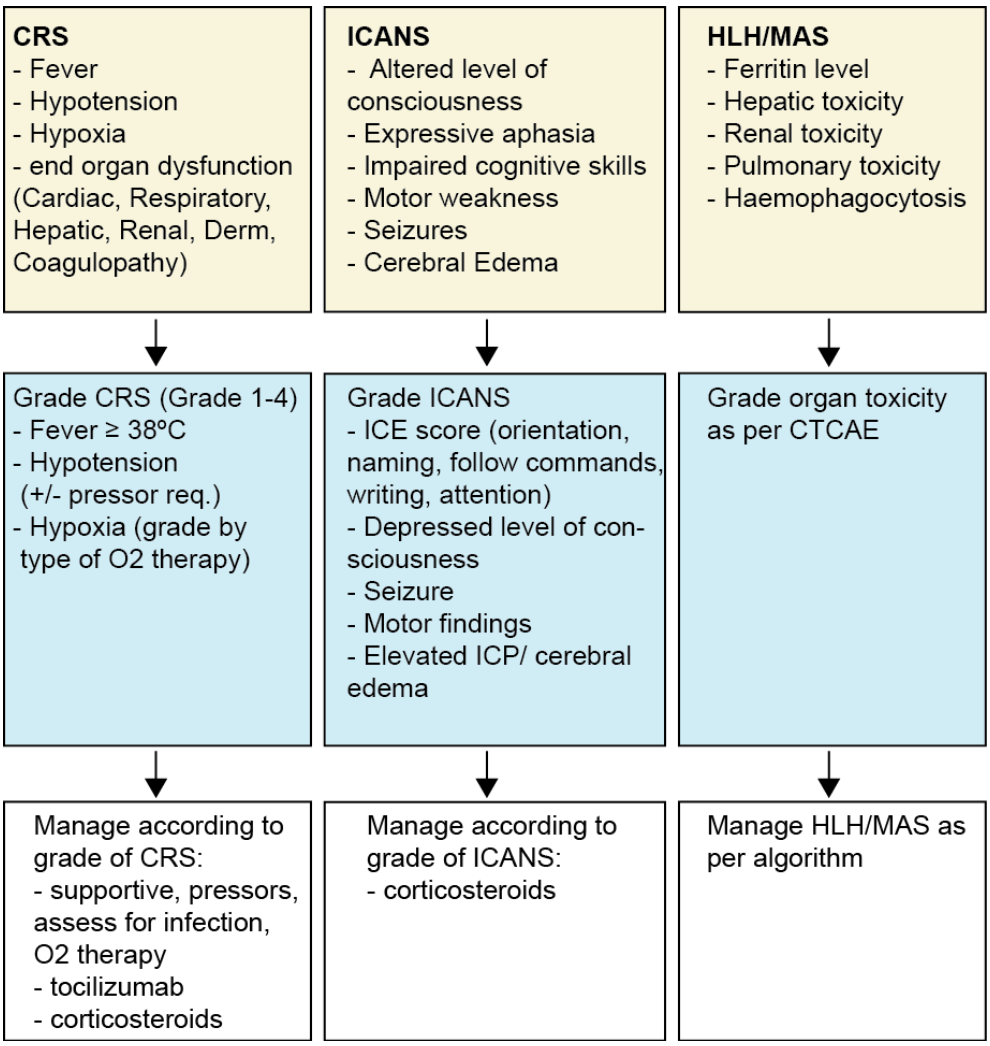
BCMA Targeting and Parkinsonism

- Rare case reports of Parkinson-like sx following BCMA CAR-T therapy. Although these sx typically present later (beyond M1), the extent/kinetics are still unknown. No known Tx but often PET-MR brain will show ↓ uptake w/in basal ganglia.

Cytopenias

- Patients will commonly have biphasic cytopenias in CAR-T. Initially following LDC, patients counts will drop as expected. In some instances patients will either have count recovery with subsequent fall vs. prolonged cytopenias that last for weeks to months. These cytopenias are commonly treated with growth factors and possibly additional immunosuppression.

Stepwise approach to assessing acute CAR T-cell toxicity:



Epidemiology:

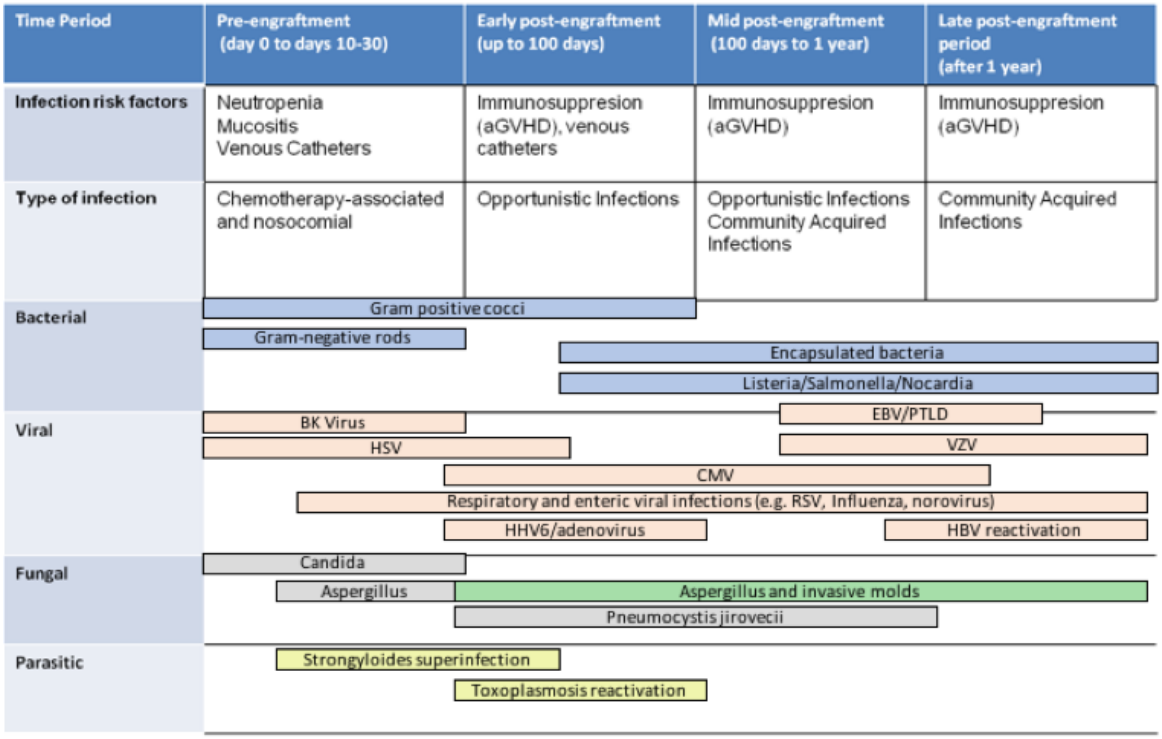
- Highest risk of infection during first 100 days and before engraftment (33-48% infected during this period, **Biol Blood Marrow Transplant 2016;22:359**)
- High risk characteristics: Age >40, High HCT Comorbidity Index, prior HCT, prior infections of donor or recipient, HLA relatedness & degree of mismatch, conditioning and graft health (ablative chemtx, graft failure), severe barrier breakdown (GVHD grades 2-4, severe mucositis, indwelling lines).

Immune reconstitution:

Following transplant, there is severe depletion of all hematopoietic cells of the immune system, especially lymphocytes. Recovery of the innate (natural) and adaptive immune systems occurs gradually during the post-transplant period. Innate immunity usually recovers over the first several months, while reconstitution of adaptive immunity takes place over the first one to two years. Risk of infection depends on how fast immune reconstitution occurs, which in part depends on both the intensity and duration of immunosuppression after allo-HCT.

Timeline of Infectious Complications:

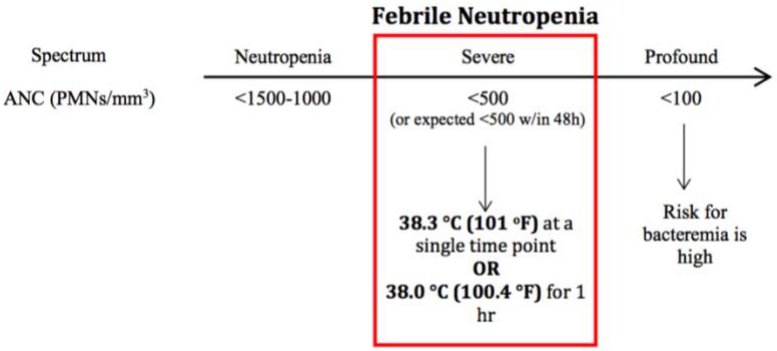
- Pre-Engraftment Period (Day 10-30): *From transplant to neutrophil recovery*
  - **Marked by nosocomial infections or preexisting colonizers**. Risks related to neutropenia (invasive fungi contingent on duration), mucositis (*Strep viridans*, enteric GNR's, HSV re-activation), lines (*Staph aureus* and CONS, *Strep*, *Candida*), and hospital exposures (*C. difficile*). Higher risk w/ myeloablative conditioning regimens due to more mucosal injury and longer neutropenia.
- Post-Engraftment period (Day 30-100):
  - **Reactivation and opportunistic infections.** After engraftment, risk applicable mainly to allogeneic tx, especially given ongoing need for immunosuppression. Risks related to acute GVHD and tx, poor T-cell repertoire (with associated infxns e.g. HSV/CMV/EBV reactivation, BK Virus, and PJP).
- Mid to Late-Engraftment period (>100 days):
  - **More community acquired pathogens**. Concern for encapsulated bacteria (*S. pneumo, N. meningitides*) and pathogens from environmental exposures. After 1 year, risk of OI significantly decreased.



Adapted from Marty FM, Baden LR (2008). Infection in the Hematopoetic Stem Cell Transplant Recipient. In: Soiffer RJ, ed. *Hematopoietic Stem Cell Transplantation*. Totowa, NJ, USA: Humana Press, 421–448.

Overview

- Risk related to myelosuppressive effects of chemotherapy, deficient humoral or cellular immunity, and mucosal barrier breakdown, which facilitate bacterial or yeast translocation.
- In febrile neutropenia without localization, organism is identified in only ~25% of cases.
- For all instances, low threshold to consult ID, especially if failure to improve on appropriate therapy, severe infection or persistent fevers in high-risk substrate, or *Staphylococcus aureus* bacteremia.



Definition:
ANC (PMN/mm3) < 500 (severe) and fever to 38.3ºC (101 ºF) at single time point or 38C (100.4 ºF) for 1 hr

- Should differentiate from:
  - **Myeloid Reconstitution Syndrome:** fever occurring after reconstitution of PMNs (note Hepatosplenic candidiasis may present during this period as well).
  - **Engraftment Syndrome:** Generally, 9-16 post-HSCT. Syndrome of fevers, rash, pulmonary infiltrates, and/or diarrhea.
- Can risk stratify using the MASCC score (Burden of illness, Hypotension, active COPD, type of cancer, dehydration requiring IV fluids, status at onset of fever, age):
  - MASCC ≥21 = Low Risk: May be treated outpatient if able to tolerate PO.
  - MASCC ≤21 = High Risk: Need inpatient treatment with IV antibiotics. Key risk factors not in score: if expected >7 d of neutropenia, ANC <100, clinically unstable.

Dx:

- History: Sick exposures; previous vaccinations; current PPX; D/R CMV and EBV status, h/o of GVHD, h/o of prior infection or colonization, h/o blood transfusions or uncontrolled malignancy (that might account for fever), comorbid conditions (decubitus ulcers, poor nutrition, foreign bodies, DM, chronic respiratory conditions, rheumatologic Dz, IBD).
- Physical Exam: skin and line site evaluation, oral cavity, lung, abdominal exam. Avoid DRE as can introduce infection and damage mucosa. Remember that w/o neutrophils, patient may only have subtle signs of infx.
- Work up:
  - BCx x 2 (1 must be peripheral culture) and if triple-lumen CVC, draw off all ports+periphery, as well as UA/urine cx, Sp Cx, CXR, Resp Viral Panel and/or Influenza/RSV/COVID19 PCR
  - Heme Malignancy/Post-HSCT: Add CMV PCR, EBV PCR, LDH, (1,3)-B-D-Glucan, and galactomannan
  - diarrhea/abdominal pain: *C. difficile* toxin, CT AP if c/f typhlitis, neutropenic enterocolitis
  - skin lesions: aspirate/biopsy. If vesicles, send for HSV/VZV PCR or culture + Ab testing
  - meningeal symptoms: CSF should also be sent for crypto Ag, HSV, CMV, VZV, and HHV-6
  - Reserve fungal markers for high-risk pts only (heme malignancy, post-HSCT, neutropenia ≥10-14 days, high risk GVHD)

Tx:

- All suggested regimens are empiric → modify per cultures, prior infectious history, MGH resistance patterns, and patient specific risk factors.
- Consider if antibiotics are bactericidal vs. bacteriostatic (prefer the former if high-risk).
- Consider GM-CSF as adjunct in neutropenic patients with prognostic factors predictive of poor outcome: long duration (> 10d) of neutropenia, severely neutropenic (ANC < 100), age > 65, PNA or other documented infection, sepsis, invasive fungal infection, prior febrile neutropenia (secondary prophylaxis), or hospitalized during development of fever.
- **Low Risk** (see risk stratification above): FLQ+Amox-clav (Clindamycin if PCN allergy)

- **High Risk**:
  - Cefepime 2 g q8h or ceftazidime 2 g q8h (MGB Renal Dosing Guideline for abnormal CrCl)
  - Allergy (Non-anaphylactic): Pip-tazo or Meropenem (See MGB PCN/Ceph Pathway)
  - Allergy (Anaphylactic): Aztreonam+Vancomycin or FLQ + Clindamycin (unless allergy to ceftazidime or on FLQ prophylaxis recently). Ceftazidime monotherapy should ***not*** be used if concerned for gram-positive infection
- **Add Antifungals** if:
  - Febrile 4-7 days on GN coverage
  - or if the patient has a new fever after defervescing on GN coverage.
  - Standard Antifungal coverage: Micafungin 100mg IV q24h. Alternative: Ambisome 3 mg/kg w/ BID BMP + prehydration
- **Add Vancomycin** if:
  - HD unstable or suspect severe sepsis.
  - Blood cultures w/ GPCs w/ pending susceptibilities, SSTI, CVC infection, or documented PNA.
  - Severe mucositis if on FLQ px or episode occurs w/ empiric Aztreonam or Ceftazidime
- **Add Anaerobic Coverage** if: Evidence of necrotizing mucositis, sinusitis, periodontal cellulitis, peri-rectal cellulitis, intraabd. infection, pelvic infection, or anaerobic bacteremia
- Discontinue antibiotics after no fever + PMN reconstitution and/or after appropriate duration for presumed source. Increasing acceptance of fixed duration of antibiotics *before* ANC recovery in patients w/o identified infectious source (see IDSA guidelines)

Overview

- Cancer and interventions (chemo/radiation, invasive procedures/indwelling catheters, immunosuppressive agents, etc.) place cancer pts at increased risk for infection, which include typical and opportunistic organisms (**Infect Dis Ther 2017;6:69**)
- New fever is a common presentation of underlying infection but must remember other causes of fever: malignancy, chemotherapy, antibiotics, VTE, blood products, etc.
- Given high infectious risk, ppx may be considered in particular circumstances. Examples include:
  - **F&N** (typically if ANC <100 for >7d): **anti-bacterial** (e.g. fluoroquinolone for GNR coverage and PsA activity) and **anti-fungal** (e.g. azole/echinocandin); frequently seen used in hematologic malignancies given prolonged neutropenia
  - **HSV**: acyclovir used, especially in HSV+ patients **undergoing alloHSCT, induction therapy for leukemia, treatment of lymphoma**
  - **CMV**: Famciclovir (broad herpesvirus activity) and letermovir (CMV-specific action), typically in **alloHSCT patients who are CMV seropositive and require GVHD ppx**
  - **Pneumocystis jirovecii**: ALL/AML, CD4 count<200, long term steroids (≥20mg prednisone equivalents qdaily for ≥2wks), prolonged neutropenia, pts receiving purine analog (e.g cytarabine). Options include TMX-SMX (preferred for efficacy but can cause bone marrow toxicity), pentamidine, or atovaquone
  - **Chronic HBV**: NRTI (e.g. entecavir) to prevent reactivation
  - Of note, use of ppx changes the epidemiology of infectious agents. For example, routine use of FQ increases prevalence of gram-positive bacterial infections seen in F&N

Bacteremia/Central Line Associated Bloodstream Infection (CLABSI)

- Epidemiology:
  - **Gram-positive**: coag-negative *Staph* > *Strep viridans* > *Enterococcus* > *Staph aureus*
  - **Gram-negative**: *E coli* > *Pseudomonas* ≈ *Klesbiella* > *Enterobacter*
  - **Emerging**: *Acinetobacter*, *Stenotrophomonas*, ESBL (but still a minority), *Candida* (esp if TPN)
  - Risk of infected line highest in: Non-tunneled central line > tunneled CVC > port. Femoral = internal jugular > subclavian (**Crit Care Med 2012;40:2479**, **Infect Control Hosp Epidemiol 2016;37:1288**)
- Presentation: Fever, erythema/purulence/pain at catheter site, altered mental status, sepsis. Immunocompromised pts may not demonstrate typical signs & sxs of infx (e.g. negative Cx, absent fever/leukocytosis/pain). Rigors a/w OR 14 for bacteremia
- Dx: BCx x2 prior to abx (at least two peripherals ideally; one set may be drawn from catheter and confirmatory if same organism grows in peripheral + catheter cx, **but high rates of contamination**)
  - Positive cx from catheter + positive peripheral cx w/ same organism = likely CLABSI
  - Positive cx obtained from catheter + negative peripheral culture = not necessarily CLABSI; could be contaminant (depending on organism)
  - 2+ BCx positive for CoNS or other commensal skin bacteria more convincing for CLABSI, if no other obvious source. **Interpretation of +BCx can be challenging as CoNS are both most common cause of CLABSI and most common contaminant**
- Tx: Ideally removal of catheter for source control if suspected CLABSI.
  - Strong indications to remove catheter:
    - Virulent organism: *Staph aureus*, *PsA, Candida, MDRs*
    - Sepsis
    - Suppurative thrombophlebitis
    - Metastatic infection (e.g. osteomyelitis, endocarditis, or if bacteremia persists after 72h of appropriate abx)
    - Line not essential
  - Empiric abx, w/ course typically defined by time of catheter removal
  - Daily surveillance BCx
  - Catheter retention/salvage may be considered in select instances such as CoNS and drug-susceptible Enterobacteriaceae. Requires antibiotic lock therapy (instillation of concentrated abx in lumen to eliminate biofilm in catheter lumen)
  - Guidewire exchange not routinely recommended as process may seed newly placed line

Enterocolitis/Diarrheal Disease

- Epidemiology:
  - *C diff* (5-20%), viruses (noro, rota, adeno, CMV), bacteria (*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*), parasites (*Cryptosporidium*, *Cystoisospora*, *Cyclospora*, helminths)

  - **Neutropenic enterocolitis (NEC)**: severe polymicrobial infiltration of intestinal wall in ~5% of hematological malignancies (Radiology 2003;226:668)
  - DDx: drug-induced (CapeIRI, FOLFOXIRI), **checkpoint inhibitor-induced**, GvHD, enteral feeding
- Presentation: Frequent liquid stools, abdominal pain, nausea/vomiting, tenesmus
- Dx: CBC, electrolytes, blood gas, *C diff*, stool O&P, blood cx (if febrile); immunocompromised: CMV PCR, stool modified acid-fast (must order *Cycloisospora* and *Cyclospora* studies as Micro Add-on); abd. pain: abd. u/s or CT A/P; EGD if c/f bleeding, GvHD, or viral colitis
- Tx: Supportive care w/ oral/intravenous hydration
  - **Abx:** usually not indicated but pathogen-specific tx should be initiated for *C. diff*, CMV, and protozoan/parasitic infections. Cefepime/flagyl if neutropenic and c/f gut translocation
  - **NEC:** bowel rest w/ NGT and nutritional support, IVF, and broad-spectrum abx w/ *Pseudomonas* and anaerobe coverage (e.g. pipercillin-tazobactam or cefepime/ceftazidime + metronidazole)

Respiratory Infections

- Epidemiology: Very high morbidity in immunocompromised hosts, e.g. acute leukemia (leading cause of death) and HSCT (80% prevalence). Pathogens implicated in non-immunocompromised cancer patients ~ general population, tx same
  - Post-obstructive PNA: Initially *Pseudomonas*, *Acinetobacter*, *Citrobacter*, *Enterobacter*, *Serratia*, *Staph aureus.* After cavity formation (4-8wks) 'SPACE-M', MRSA, anaerobes, and *Aspergillus*
  - Immunocompromised or on chronic corticosteroids (>1 mo of prednisone ≥20 mg): PJP, *Nocardia*, *Legionella*, *Mycobacterium*, CMV, molds, and endemic mycoses (Chest 2012;141:442)
  - DDx: aspiration, PE, GvHD, idiopathic interstitial pneumonia, bronchiolitis obliterans w/ organizing pneumonia (BOOP), and diffuse alveolar hemorrhage (DAH)
- Presentation: Cough, dyspnea, fever/chills, pleuritic chest pain, rales/crackles/rhonchi
- Dx: CXR, sputum smear/cx, RVP, influenza/RSV and COVID-19 PCR, Legionella Ag, 1,3-β-D-glucan, galactomannan, CT chest, BAL if required
- Tx: Standard CAP/HAP therapy if non-immunocompromised
  - Neutropenic patients may require abx active against *Pseudomonas* (cefepime, pip-tazo, meropenem) and 'SPACE-M' organisms
  - Post-obstructive: relieve obstruction + long-term IV abx w/ activity against *Pseudomonas* and anaerobes (MTZ/clinda) +/- anti-MRSA or antifungals
  - fungal infection: **resection** if needed + anti-fungal agent w/ activity against Aspergillus and other molds, typically amphotericin B or voriconazole/posazonazole. +/-Echinocandin (e.g. micafungin) can be added

Meningitis

- Epidemiology: Coag-negative *Staph* > *Staph aureus* > *Cryptococcus* > *Enterococcus* ≈ GNRs > *Listeria*/*Neisseria.* Risk factors: **prior neurosurgery**, head/neck malignancy, hematologic malignancy. CSF studies demonstrate significantly lower WBC count in onc patients. DDx: carcinomatous meningitis, drug toxicity, skull base/brain metastasis, CNS vasculitis
- Presentation: Fever, headache, AMS, focal deficits, nuchal rigidity, seizure. Classical triad of fever, nuchal rigidity, and mental status change **only ~5% of onc patients** (Medicine 2017;96:19)
- Dx:
  - LP (gram stain, diff, glucose, protein, HSV/VZV PCR), blood cx x2, *Cryptococcus* Ag
  - CSF: WBC >10, protein >40, glucose <40 or CSF/serum <0.6, opening pressure usually <200
  - ***Immunocompromised patients w/ focal neurological deficit, AMS, papilledema, new seizure, or CNS disease (or high risk for CNS disease) require CT head prior to LP (to assess risk of catastrophic cerebral herniation)***
- Tx:
  - Blood cx → empiric abx → CT → LP
  - Empiric anti-microbials: vancomycin + cefepime/ceftazidime/meropenem, IV acyclovir, +/- ampicillin
  - Adjunctive dexamethasone is of greatest benefit in pneumococcal meningitis w/ AMS (~3% of cases in oncology pts)

Skin and Soft Tissue Infection (SSTI)

- Epidemiology (SciWorldJournal 2012:804518):
  - *Pseudomonas* = *E coli* = *Staph aureus* > coag-negative *Staph*
  - Cellulitis/erysipelas > abscess > exit-site/tunnel infections
  - **Ecthyma gangrenosum**: characteristic necrotic ulcer a/w *Pseudomonas* bacteremia in immunocompromised/neutropenic patients

  - Risk factors: recent chemo/XRT, prior invasive procedure, prior abx, prior transfusion, CVC
  - DDx: DVT, drug reaction, dermatitis (e.g. from XRT), lymphedema, herpes zoster
- Presentation: Erythema, swelling, localized pain; fever present in 64% of patients
- Dx: Wound cx, CBC, BCx x2; imaging: CT or U/S evaluation of suspected abscess; XR/MRI if concern for osteomyelitis
- Tx: Wound cx from purulent SSTIs grow MRSA in ~45% of general patients. I&D when indicated + IV abx w/ activity against *Pseudomonas* and resistant GPCs until cx results available

Infective Endocarditis (IE)

- Epidemiology:
  - *Streptococcus* = *Staph aureus* > coag-negative *Staph* > *Enterococcus* > *Candida* (Arch Intern Med 2009;169:463)
  - Sources of bacteremia: CVC > GI > GU
  - DDx: CLABSI, ACS, myopericarditis, progressive valve disease, cardiomyopathy, cardiac device infection, osteomyelitis
- Presentation:
  - Fever (90%), cardiac murmurs (85%), weight loss, malaise, headache, nocturnal diaphoresis
  - Janeway lesions: non-tender erythematous macules on the palms and soles (microabscesses)
  - Osler nodes: painful violaceous lesions on pads of fingers/toes (immune complex deposition)
  - Roth spots: retinal hemorrhages (immune complex deposition w/ vasculitis)
- Dx: **Modified Duke Criteria** developed for patients w/ left-sided native valve IE (2 major *or* 1 major + 3 minor *or* 5 minor):
  - major: (1) pos BCx w/ typical IE organism, (2) e/o vegetation on TTE/TEE
  - minor: (1) predisposing heart condition or IV drug use, (2) fever, (3) vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhage, Janeway lesions, (4) immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor, (5) positive BCx w/ organism not typical for IE
  - BCx x3 at separate venipuncture sites, TTE (75% sensitive) → TEE (90% sensitive), baseline EKG + tele, CXR to evaluate for septic emboli or congestion
  - Repeat blood cx q24h until negative
- Tx:
  - Abx therapy can usually be delayed until BCx results in pts without acute symptoms
  - If acutely ill and BCx not yet resulted: empiric vancomycin/CTX; consider daptomycin/linezolid if c/f VRE, cefepime for PsA, anti-fungal (amphotericin or echinocandin) for Candida

Special Considerations

- Hairy cell leukemia: *Mycoplasma* infection
- Multiple myeloma: invasive streptococcal disease & other encapsulated bacteria

SUMMARY OF EMPIRIC THERAPY FOR INFECTIOUS SYNDROMES IN ONCOLOGY PATIENTS

Infectious Syndrome	Initial Diagnostics	Empiric Tx
Bacteremia	BCx (peripheral + each lumen of catheter)	Vancomycin + cefepime; strongly consider line removal
Diarrheal Dz	CBC, lytes, *C diff*, stool O&P; consider CT AP	Rehydration; if c/f **NEC**: pip-tazo or cefe/ceftaz + MTZ
Respiratory Infections	CXR, sputum, RVP/flu/RSV, Legionella, 1,3-β-D-glucan, galactomannan; Further imaging w/ CT chest +/- BAL	[azithro + CTX] or levofloxacin for CAP; [vanc + cefe/pip-tazo/mero] for HAP; consider fungal coverage if **HM/post-HSCT** consider anaerobic/fungal coverage if **post-obstructive**
Meningitis	BCx x2 → empiric abx → CT → LP; ***All onc pts CT head prior to LP***, Cryptococcus Ag	Vancomycin 15-20 mg/kg q8-12h + cefe/ceftaz/mero; ampicillin for *Listeria,* acyclovir for HSV Amphotericin + flucytosine for Cryptococcus
SSTI	Wound Cx, peripheral BCx x2, CBC, CT or U/S for abscess	If septic: vanc + pip-tazo + clinda & call ID; If neutropenic & stable: vanc + cefe
Endocarditis	Peripheral BCx x3, TTE, EKG, CXR	If acutely ill: empiric Vancomycin/CTX w/ special considerations to additionally cover VRE, PsA, Candida

Epidemiology

- There is an estimated 1.8 million new CA cases in the US in 2020, w/ an estimated 606,520 deaths in 2020 2/2 CA.
- Most common new dx's in US: breast, lung, prostate, colorectal, melanoma, bladder, NHL, kidney and renal pelvis, uterine, leukemia. The mortality/morbidity of these CAs varies significantly.
- Most frequent CA death: lung/bronchial, colorectal, pancreatic, breast, prostate.

Cancer-Specific Screenings

Breast Cancer:
Guidelines on when to start screening for women at average risk for breast CA vary (below are the guidelines from PCOI based on USPSTF, ACS, ACOG, and CRICO).

- Age 40+: Individualized discussion of when to begin screening women ages 40, 45, or 50 and to screen annually vs biennially.
- Age 45 or 50-55: Mammogram every 1-2 yrs.
- Age 55-74: Mammogram at least every 2 yrs.
- Age 75+: Discuss individual risk/benefit assessment for mammogram, which may be beneficial in older women w/ 10+ year life expectancy.
- Benefit of clinical breast exam for women of any age is unclear, as screening results in increase in false positives w/ no e/o change in breast CA outcomes in patients getting regular mammography.
- While self-awareness of changes in the breast is encouraged, patient education regarding self-exams is controversial.

Note that many women do not fall into the average risk category and may require more intensive screening (including using MRI as an adjunct to mammography) and/or screening at an earlier age, including women w/:

- A hx of breast CA, lobular carcinoma in-situ (LCIS), or atypical breast hyperplasia
- Higher risk for CA based on the Gail model or the IBIS Tool (breast CA risk assessment tools)
- A hx of radiation to the chest
- Genetic predisposition to CA (i.e. BRCA mutation as well as others) or ↑ risk based on family hx risk calculators (esp. those w/ >20% lifetime risk)

Note: Clinicians should maintain a low threshold to refer patients w/ concerns about a lump or irregularity to a breast surgeon, regardless of mammogram findings.

Cervical Cancer:
Women at average risk for cervical CA should begin screening w/ Pap smears q3yrs starting at age 21. Women ages 30+ can choose to undergo HPV DNA testing + cytologic testing. If both are negative, the screening interval can be lengthened to q5 yrs. Women who may stop after 65 include those w/o a hx of CIN2-3 in the past 20 yrs and w/ adequate prior screening (3 documented, consecutive, negative paps or 2 negative HPV tests in prior 10 yrs w/ most recent test w/in last 5 yrs). Screening should also be stopped for those s/p complete hysterectomy (removal of the cervix w/ no cervical cuff remnant) who have no hx of cervical CA or CIN2-3 w/in past 20 yrs.

Screening should be performed more frequently in women w/ strong risk factors for cervical CA, including in utero DES exposure, HIV+, immunocompromised state, and a hx of cervical CA.

Colorectal Cancer:
USPSTF currently in process of updating recommendations. Draft recommendation at this time includes:

- Grade A: 50-75y –recommends screening for CRC.
- Grade B: 45-59y –recommends screening for CRC.
- Grade C: 76-85y –recommends clinicians selectively offer screening, as evidence indicates net benefit in age group is small, so must consider patient's overall health and prior screening hx.

Risk assessment: Age is one of most important risk factors, as nearly 94% of cases occur in 45y and older (although incidence is rising in young adults). Rates also higher in black adults, persons w/ family hx of colorectal CA, and men. Even in absence of risk factors, patients 45y+ should be offered screening.

General population screening:

- visual exams: colonoscopy Q10y (alternative: CT colonography Q5y, flex sig Q5y, or flex sig Q10y + FIT Q1y)
- stool-based tests: fecal immunochemical test (FIT) Q1y, high sensitivity guaiac-based fecal occult blood test (HSgFOBT) Q1y, multi-targeted stool DNA test Q1 to 3y

At-risk population screening:

- Personal hx of polyps: time of re-testing depends on #, size, and character of polyp (Gastroenterologist who performs the colonoscopy often helps inform when next colonoscopy should be done)
- Family hx: CRC in any first degree relative <60 yo or in 2 or more first-degree relatives at any age– start screening colonoscopies at age 40 or 10 yrs before the youngest case (whichever earlier)
- IBD: colonoscopy ≥8y after onset of symptoms, then q1-3y w/ biopsies.
- HNPCC/Lynch or FAP: start screening at age 20-25 or 5 yrs before youngest case in family, then q1-2y w/ biopsies; genetic testing should be offered to relatives.
- FAP: start screening at age 10-12 w/ sigmoidoscopy or colonoscopy Q1-2y. Yearly colonoscopies once polyps are found until a colectomy is planned.

Lung Cancer:

USPSTF recently updated guidelines in 2021.

- Grade B: 50-80y w/ a 20 pack-year smoking hx and currently smoke or have quit w/in past 15 yrs –annual screening for lung CA w/ low-dose CT. Screening should be discontinued once a person has not smoked for 15 yrs or develops a health problem that substantially limits life expectancy or ability/willingness to have curative lung surgery.

In 2015, Medicare announced it would cover low-dose lung CA screening CT scans for eligible high-risk patients ages 55-77. However, they required a documented face-face shared decision-making visit before initial screening exam, as well as smoking cessation counseling. PCOI has available tools to facilitate these dicsussions. Given the recency of these new guidelines, insurance companies may lag behind in their coverage of the newest recommended ages to initiate screening, so it will be important to encourage patients to discuss w/ their insurance company until the guidelines have been widely accepted.

Prostate Cancer:

The USPSTF currently recommends patient-centered decision-making regarding PSA-based screening for men ages 55-69 yo (grade C) and no screening for men age 70+ (grade D) (**JAMA 2018;319:1901**).

> **Benefit**: PSA screening 1) may reduce the risk of advanced-stage prostate CA (**Eur Urol 2012;62:745**) and 2) confers at most a small absolute benefit in reducing prostate CA mortality (**Lancet 2014;384:2027**).
>
> **Harm**: PSA screening could lead to overdiagnoses and false-positive PSAs, which in turn, may lead to anxiety and morbidity related to surgical and radiation therapy (e.g., urinary incontinence, erectile dysfunction, bowel dysfunction).

Tools for shared decision-making, including a video available to patients, can be found through PCOI and the MGH Blum Center for Patient and Family Learning.

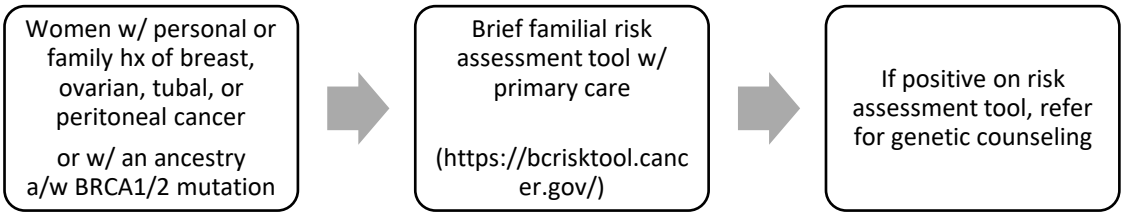
Source	Tool(s)	Age(s) to screen	Testing Intervals	Biopsy Indication
NCCN (2018)	PSA + DRE	After shared decision making: • 45-75 yo • >75 yo (only in very healthy men, otherwise discouraged)	Assuming normal DRE: • If PSA <1, then 2-4 yrs • If PSA 1-3, then 1-2 yrs	PSA >3 or very suspicious DRE
ACS (2019)	PSA +/- DRE	After shared decision making: • >50 yo w/ life expectancy >10 yrs • >45 yo at high risk (African American/Black; first-deg relative w/ prostate CA diagnosed before 65 yrs of age) • >40 yo at very high risk (>1 first-deg relative w/ prostate CA at early age)	Assuming normal DRE: • If PSA <2.5, then every 2 yrs • If PSA >2.5, then every 1 yr	Not discussed

AUA (2018)	PSA	After shared decision making: • 55-69 yo Not recommended for: • <55 yo • >70 yo w/ life expectancy <10-15 yrs	• 2 or more yrs	Consider for PSA >3 after repeat confirmatory test + consideration of additional factors affecting PSA levels

Screening for Genetic Predispositions to Cancer

There are many genetic syndromes (including BRCA1/2, Li-Fraumeni, Cowden's syndrome, FAP, Lynch, MUTYH-associated polyposis, serrated polyposis syndrome, Peutz-Jeghers) that can increase an individual's CA risk and taking a personal and family hx is key to detecting patients who may require additional screening or referral to a genetic counselor.

- USPSTF recommendation for BRCA-related CA Risk Asssessment & Genetic Counseling/Testing (uspreventiveservicestaskforce.org):



- Genetic testing should be considered in patients w/ a family hx of multiple primary breast CAs, breast CAs diagnosed younger than age 46, women of Ashkenazi descent w/ a hx of breast, ovarian, or pancreatic CAs in their families, or women w/ family histories of at least three tumors and/or macrocephaly and/or dermatologic signs of Cowden's syndrome (Genetic/Familial high-risk assessment: Breast and Ovarian. NCCN Guidelines, 1.2018)

Risk-reducing Medications and Surgeries

- CRC: The use of ASA for primary prevention remains an area of judgment requiring individualized consideration of risks/benefits. The USPSTF recommends consideration of ASA for prevention of both colorectal CA and cardiovascular dz in those adults ages 50-59 w/ a >10% risk of CVD over 10 yrs and a low risk for bleeds (Grade B). The decision for adults ages 60-69 must be individualized (Grade C). Some clinicians will choose to use a cut-off of 7.5% ASCVD risk, similar to that used for statins. The American College of Chest Physicians (2012) similarly recommends ASA for primary cardiovascular prevention in patients over age 50, again weighing individual bleeding risks.
- Breast CA: Risk reduction strategies recommended by the USPSTF for women ≥35yo at ↑ risk for breast CA may include lifestyle modification (e.g., exercise), medications (e.g., tamoxifen, raloxifene, aromatase inhibitors), and surgeries (e.g., mastectomy, salpingo-oophorectomy for women). Options depend on BRCA status.

Other Risk Reduction Strategies

- Vaccinations, lifestyle modification, and avoidance of carcinogenic exposures also contribute to CA prevention.
- Globally, it is estimated that 35% of CAs are due to obesity, low fruit/vegetable intake, inactivity, smoking, EtOH use, unsafe sex, air pollution, indoor air contamination from solid fuels, and injections → hep B/C exposure (**Lancet 2005;366:1784**).
- Vaccinations: HPV is not only implicated in cervical CA, but also head and neck tumors, anal CAs, and penile CAs. The vaccine is recommended for all men and women up to age 27 and now available up to age 45, depending on factors such as likelihood of prior exposure.
- Lifestyle factors: Excess weight accounts for 15-20% of CA mortality (**J Clin Oncol 2014;32:3568**); tobacco exposure (80% of lung CA in males and 50% in females: CA)(**Cancer J Clin 2011;61:69**); ETOH use (chronic ETOH may account for up to 3.6% of CAs)(**Nat Rev Cancer 2007;7:599**); red meat consumption; occupational disruption of circadian rhythms.

- Chemical exposures: benzenes, nitrosamines, asbestos, formaldehyde, soot, coal, wood dust, aflatoxins. The International Agency for Research on Cancer (IARC) lists over 100 carcinogenic substances and occupational exposures (**J Natl Cancer Inst 2011;103:1827**).
- Viral/ bacterial exposures: Treatable: H. pylori, HBV/HCV, HIV. Vaccines available: HPV, HBV.
  Other: EBV, HTLV-1.
- Iatrogenic: Radiation, hormone tx, immune suppression, chemotherapy.

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Approach to New Cancer Diagnoses:

- The first steps include determining the pathologic diagnosis ("tissue is the issue") and cancer stage. Involve oncology consultants early if there are questions about where and how to biopsy, what molecular tests should be run on tissue, or which imaging to determine staging.
- Solid tumors are commonly staged through the "TNM" (Tumor-Node-Metastasis) system, which uses information regarding the size of the primary tumor, the number and/or location of nodal metastases, and the extent of other metastatic spread to assign tumors to stages I-IV.
- Cancer treatments may involve surgery, radiation, and/or systemic therapy, which includes chemotherapy, targeted therapy, immunotherapy and/or hormonal therapy. Symptom control and other supportive measures also play an important role.
- Multidisciplinary decisions regarding treatment depend not only on patient's tumor pathology and stage, but also their performance status (a measure of the patient's ability to carry out normal activities despite their disease). Two main scales are the **Karnofsky** Scale (0-100, with 100 being fully active and 0 being deceased) and the **ECOG** scale (with 0 being fully active and 5 being deceased).

Chemotherapy:

- Chemo can be used as a primary treatment modality, before or after surgery (as **neo-adjuvant** or **adjuvant** therapy, respectively), or concurrent with RT, usually as definitive treatment.
- Many cytotoxic chemos inhibit cellular multiplication causing toxicity to rapidly dividing cells (e.g. bone marrow cells → cytopenias, mucosal cells → mucositis and GI symptoms, hair cells → alopecia). Examples include alkylating agents, anti-metabolites, microtubule and topoisomerase inhibitors, and free radical producers.
- Toxicities vary by regimen, but may include: BM toxicity (cytopenias), n/v/d (antiemetic prophylaxis used for some regimens), mucosal toxicities (mucositis), cardiac toxicities (CM, QTc prolongation, myopericarditis), pulmonary (pneumonitis/ILD), renal, neuro (including peripheral neuropathies, cerebellar ataxia, encephalopathy), GI (LFT abnormalities, including VOD), dermatologic (including palmar-plantar erythema), allergic rxns, and infertility.
- Combination chemotherapy regimens maximize response rate while increasing potential toxicity. They are therefore usually reserved for treatment of cancer in the curative setting whereas single-agent chemo regimens are used palliatively.

Targeted therapies: Target molecular pathways and overexpressed byproducts. These agents include monoclonal antibodies, small molecule inhibitors (e.g. tyrosine kinase inhibitors), and monoclonal antibodies conjugated to cytotoxic therapies.

- Targets include growth factor receptors and their ligands (e.g. EGFR, Her2, VEGFR), tyrosine kinase signaling (e.g. Bruton tyrosine kinase, ALK), serine/threonine kinase pathways (e.g. RAF, PI3K/mTOR, and MAPK), fusion proteins (BCR-ABL), angiogenesis inhibitors (e.g. anti-angiopoeitin), and proteasome inhibitors, among others.
- Because of the targeted nature of these therapies, they are usually discontinued in the setting of tumor progression (indicating resistance). Since many of these agents are very new and can cause rare toxicities; it is important to talk with a patient's oncologist about whether to continue these therapies when patients are inpatient.

Immunotherapy: T-cell activation is normally held in check by CTLA-4 and PD-1. Certain tumors can downregulate T-cell activation by upregulating CTLA-4 and PD-1/PD-L1 signaling, leading to blunted immune responses. Checkpoint inhibitor therapies, which restore T-cell activation, are an especially successful form of immunotherapy, leading to durable responses in certain types of tumors (e.g. melanoma, renal cell, and lung CA). Response can correlate with the burden of tumor "neoantigens", or misfolded proteins expressed on tumor cells which allows T-cells to identify them as foreign. Commonly used checkpoint blockade drugs include ipilimumab, pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab. These medications are associated with several toxicities that may require prompt initiation of immunomodulatory medications, including: pneumonitis, colitis, hypophysitis, thyroiditis, adrenalitis, hepatitis, rash, renal toxicity, and neurologic side effects (both peripheral and central). See **Section 9.6**

Surgery: Surgery can play an important role in obtaining tissue for dx, staging, curative extraction of tumors, palliative debulking, and cancer prevention in patients with genetic syndromes. Surgical therapy not only improves response rates through en bloc resection, but also because larger tumors are more prone to having multiple clones leading to resistance to medical therapy, as well as hypoxia leading to resistance to radiation therapy. Surgical techniques aim to ensure clean margins and prevention of seeding through adequate resection of surrounding tissue.

Principles of Clinical Trials:

- Phase 0 – very low doses, given to a small number of subjects to test pharmacodynamics/ pharmokinetics
- Phase I – assesses drug toxicity at escalating doses, while further assessing pharmacodynamics/ pharmokinetics
- Phase II – assesses treatment safety and efficacy in larger cohort

- Phase III – assesses treatment efficacy relative to existing standard of care, typically through randomization
- Phase IV – post-approval studies including of long-term toxicities

Autopsy Studies: Autopsy studies have proven important for assessing mechanisms of disease progression. Some molecular studies may require "warm" or "rapid" autopsies initiated within hours of a patient passing away. At MGH, these can be arranged by paging the rapid autopsy pager.

Survivorship: The increasing number of patients surviving cancer require monitoring for cancer recurrence, secondary malignancies, and other sequelae of cancer treatment.

- Cardiovascular dz is a leading cause of mortality and morbidity in survivors, including effects of chemo and/or RT exposure.
- Risk reduction (smoking cessation, healthy lifestyle) is critical.
- The NCCN survivorship assessment includes a patient questionnaire with domains for cardiac toxicity; anxiety, depression, and distress; cognitive function; fatigue; menopause; pain; sexual function; sleep disorder; healthy lifestyle; immunizations and infections.
- Other long-term complications may include endocrinopathies, lymphedema, bone loss, pneumonitis, immune dysregulation, and infertility.

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Background

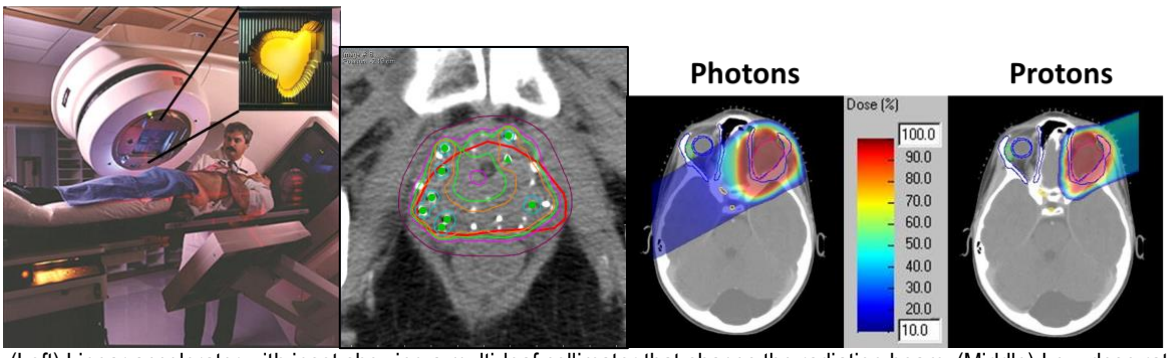
Radiotherapy (RT) came into routine use in the treatment of cancer in the early 1930s.[1] Today, more than half of all cancer diagnoses have an indication for RT with either curative or palliative intent.[2,3] While RT can be curative on its own in some settings (e.g., cervical, head & neck, and prostate cancers), it is most often combined with surgery and/or chemotherapy in a multidisciplinary fashion. Modern radiotherapy techniques are sophisticated, with the ability to deliver effective doses of radiation to tumors with submillimeter accuracy while avoiding toxicity profiles seen with older methods.[4] In this way, while RT is not molecularly targeted, it is spatially targeted with great precision.

What is radiotherapy (RT)?

There are two major forms of RT: external beam radiotherapy (EBRT) and brachytherapy. The most common form of EBRT uses high-energy photons (megavoltage X-rays); by contrast diagnostic radiology uses low-energy X-rays (kV). The other major modality of EBRT is particle therapy such as electrons (widely available), protons (available at MGH in New England), and carbon ions (available in Europe/Japan). Particle therapy has some physical advantages, most notably the ability to "stop" after traversing a certain depth of tissue.

There are several common EBRT delivery techniques you may encounter. In order of increasing conformality (decreasing exposure of surrounding normal tissue to high-dose radiation): (1) 2D, (2) 3D conformal (3DCRT), (3) intensity-modulated RT (IMRT), (4) volumetric-modulated arc therapy (VMAT), (5) stereotactic radiosurgery (SRS) or stereotactic body radiation therapy (SBRT). 2D and 3D conformal techniques are faster to design and therefore well-suited for palliative or urgent treatments. The more conformal techniques are typically utilized in definitive settings where higher RT dose is required and cancer cure is the goal. SRS and SBRT are used for ablation of metastases or small primary tumors.

Brachytherapy involves image-guided placement of radioactive sources into a tumor through an interventional procedure typically performed under anesthesia in an operating room. The source can be permanent (low-dose rate; implanted seeds) or temporary (high-dose rate; source delivered by robotic afterloader into catheters placed by radiation oncologist). Because of rapid dose falloff, brachytherapy can often significantly escalate doses to the tumor while minimizing dose to surrounding tissues.



(Left) Linear accelerator with inset showing a multi-leaf collimator that shapes the radiation beam. (Middle) Low-dose rate prostate brachytherapy showing high conformality of isodose lines. (Right) Comparison of photon and proton dosimetry to treat a left orbit tumor. Note the lack of an exit dose with the proton plan.

How does it work?

Standard photon-based RT is delivered with a linear accelerator (LINAC), which accelerates electrons in a waveguide, which then collide with a heavy metal target to produce high-energy X-rays. The ionizing radiation then interacts with water in tissues to create free radicals that generate DNA breaks. Single strand DNA breaks are easily repaired, whereas double strand DNA breaks are difficult to repair, leading to cell death through mitotic catastrophe, apoptosis, necrosis, senescence, and autophagy. The standard radiation unit of dose is the Gray (Gy) = 1 Joule of energy deposited per kilogram of tissue.

How can an effective dose of radiotherapy be delivered while minimizing side effects?

The effect of RT on tumor and normal tissue depends on cell turnover rate and capacity to repair sub-lethal damage from RT (quantified by α/β ratio). Normal cells generally have greater capacity to repair DNA damage, especially when we use modern, highly conformal RT techniques to reduce the volume of normal tissue treated and spread out dose over time (fractionation). The total dose is delivered in multiple small daily doses, usually 1.8-2 Gy/fraction for curative treatments (total time usually 4-8 wks) and ≥3 Gy/fraction for palliative treatments and SRS/SBRT (total time usually 1 day – 3 wks). In the simplest designs, the same

dose is delivered to the same treatment volume for every fraction. In some cases, different regions of the treatment volume have different risks (e.g., gross vs microscopic disease) and there are two strategies to address this: (1) treat the entire volume to a certain dose and then "cone down" to the smaller high-risk volume for the remainder of the delivered dose, or (2) use advanced techniques to "dose paint" these regions differentially such that the high-risk region receives a higher dose per fraction than the low risk region. Radiation oncologists integrate multiple factors when determining how to best design the dose, fractionation, and treatment volumes including patient performance status, comorbidities, characteristics of surrounding organs at risk, and tumor properties (e.g., size, radiosensitivity).

What are the side effects?

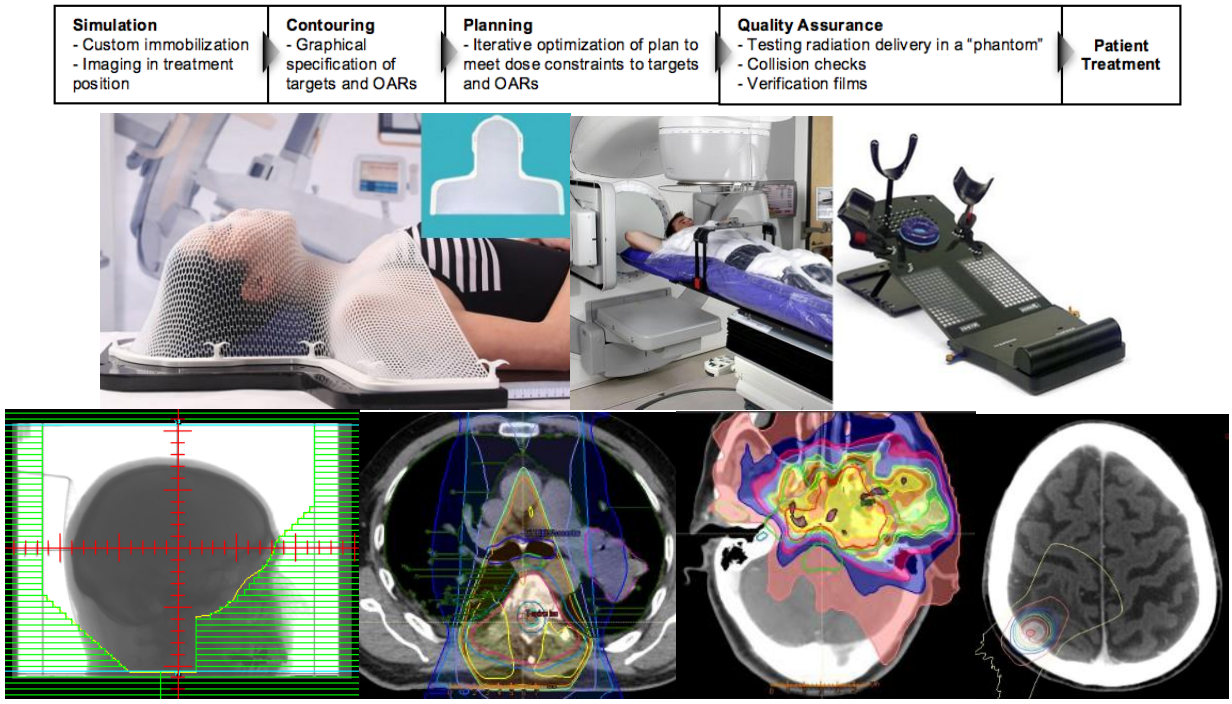
Radiation side effects are related to total dose to normal tissues, volume of normal tissue treated, characteristics of the normal tissue (e.g., small bowel has high cell turnover whereas spinal cord has very low cell turnover), and patient factors such as age. They can be divided into acute and chronic effects. Acute effects develop gradually over the course of treatment (inflammatory) and resolve within days to weeks of completion. Chronic effects occur months to years after completion of RT (fibrotic) and may be permanent. The table below lists selected radiation-associated adverse effects and normal tissue tolerances:

Selected radiation-associated adverse effects and normal tissue tolerances at 1.8-2 Gy/fraction. Concurrent chemo may reduce these tissue tolerances and exacerbate adverse effects. Vn = volume of organ receiving at least n Gy.

Organ	Tolerance	Adverse Effects
General	---	Fatigue
Skin	V20 <50%	Erythema/desquamation/alopecia
Spinal cord	45-50 Gy	Myelitis/paralysis
Optic chiasm/nerves	54 Gy	Optic neuropathy
Lens	6-10 Gy	Cataracts
Lung	V20 <30%, mean <17 Gy	Pneumonitis
Heart	Mean <20 Gy	Pericarditis/CAD
Liver	V30 <30%	Hepatitis
Kidneys (bilateral)	V20 <30%, mean <15 Gy	Renal dysfunction
Esophagus	Mean <34 Gy	Esophagitis
Small bowel	V45 <195 cc	Enteritis/diarrhea
Bladder	V70 <30%	Cystitis

Radiation Oncology Workflow

For inpatient consults who need urgent treatment, 2D and 3DCRT are the two techniques you will most commonly encounter. Before any patient can be treated with RT, they must undergo a simulation ("mapping") session during which the patient is immobilized (usually supine, sometimes prone) in a manner that is reproducible, enables anticipated beam angles without interference from uninvolved limbs/body regions, and is relatively comfortable. Without immobilization, treatment precision is compromised. The patient is imaged (2D = fluoroscopy, 3DCRT = CT scan) in the treatment position, and the radiation oncologist uses these images to graphically specify the treatment target(s) and organs at risk (OAR) and the dose constraints that apply to each. This clinical plan then goes to a team of dosimetrists and physicists who iteratively generate a series of plans specifying the number of beams, beam angles and shapes, and weighting factors. There is often a compromise between target coverage and OAR protection and the radiation oncologist reviews each plan and directs the optimization process based on the clinical scenario. After a plan is created, it goes through a quality assurance process. Only after all of these steps are completed does patient treatment begin. For simple 2D plans, treatment can usually begin within one day. 3DCRT plans with more complex beam arrangements require approximately 2-3 days to design and test, whereas the most complex IMRT/VMAT/SRS/SBRT treatments take at least 5-7 days.



(Top) Flowchart of general radiation oncology workflow. (Middle) Examples of immobilization devices. (Bottom) Examples of 2D, 3DCRT, IMRT/VMAT, and SRS plans from left to right.

Practical Information

Consulting Radiation Oncology

- Weekdays (M-F 9-5 pm): 617-726-1526
- Weeknights and weekends: on-call resident (p21807)
- Place Epic order "Inpatient Consultation to Radiation Oncology"
- When you call an inpatient consult during the day, you will speak with an administrator who will need information from you to triage the patient to the correct service (Radiation Oncology is divided into site-specific services, each covered by a different resident).
- When you speak with the Radiation Oncologist, please have the following information ready:
  - Code status
  - Relevant psychosocial complications or medical comorbidities
  - Oncologic diagnosis (if metastatic, what is the primary or is it unknown)
  - Reason for consult: symptoms, urgency, site(s) for potential treatment
  - How much does the patient know about their diagnosis? What has been shared with them?
  - What evaluation has been done and what tests are planned?
  - What other relevant teams have been consulted (e.g., medical oncology, surgery)?
  - What other oncologic treatment has the patient received?
  - Has the patient ever received RT before? If so, is the prior treatment information available?

IMPORTANT: A pathological confirmation of malignancy is NOT required to consult Radiation Oncology in urgent situations. In fact, it is good to involve Rad Onc early in the workup because the imaging studies and diagnostic tests helpful for deciding if and how to treat with RT may be different than what Medical or Surgical Oncology request.

Indications for Urgent/Emergent RT

- Brain metastases or leptomeningeal disease with progressive neurologic dysfunction
- Symptomatic spinal cord compression
- Peripheral nerve compression with progressive neurologic dysfunction
- Superior vena cava syndrome
- Bleeding (e.g. hematuria from prostate CA; note RT is not effective for arterial bleeding → consult IR/surgery)
- Malignant airway obstruction

Emerging Applications of Radiotherapy

Immune checkpoint inhibitors (IO) have transformed the management of a wide range of advanced malignancies, but most patients do not respond. There is increasing evidence that RT has myriad effects on the immune system including release of damage-associated molecular patterns and cytokines, increased presentation of tumor neoantigens on antigen-presenting cells, and diversification of the host T-cell repertoire. Under certain circumstances, RT may synergize with IO to augment the anti-tumor response and improve clinical outcomes.[5,6] In patients with oligometastatic progression (no more than 3-5 mets) on systemic therapy, aggressive local therapy (RT or surgery) to all sites of gross disease may improve outcomes and/or enable continuation of an otherwise effective systemic therapy.[7-9] Research into the optimal role of radiotherapy in these settings is ongoing.

Summary

- Radiotherapy is a safe and highly effective tool in the management of cancer.
- Most patients with cancer will receive RT at some point during their treatment course.
- We encourage early consultation of Radiation Oncology for those patients who are admitted with symptoms related to their malignancy. This is particularly critical for patients with rapidly progressive symptoms, including symptomatic brain metastases or cord compression.

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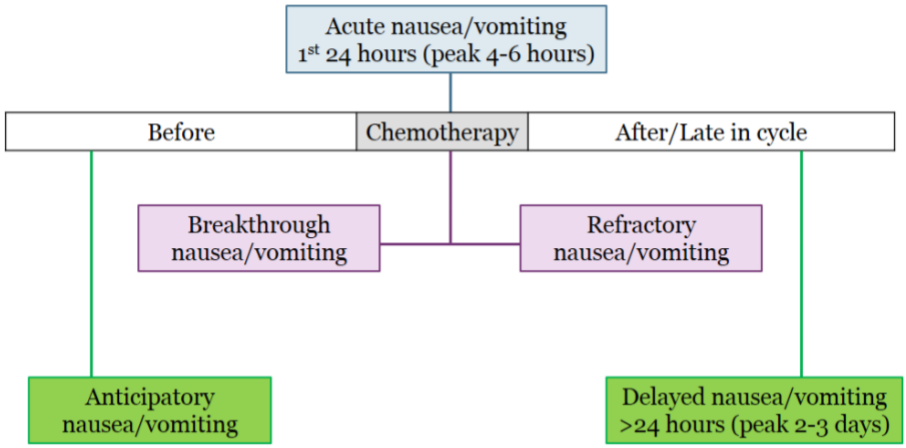
Background (NEJM 2008;358:2482)

Chemo-Induced Nausea/Vomiting (CINV) Types

Type	Time frame/Onset	Definition
Acute	Within 24 hours	• CINV that occurs within 24 hours of chemotherapy administration
Delayed	After 24 hours	• CINV that occurs 24 hours after chemotherapy administration. • Can be difficult to treat
Anticipatory	Prior to chemo administration	• CINV prompted prior to chemotherapy administration • Usually due to past poorly controlled CINV or anxiety about chemotherapy
Breakthrough	After chemotherapy administration	• CINV that occurs despite prophylactic CINV medications
Refractory	After chemotherapy administration	• CINV that occurs despite prophylactic CINV medications and rescue CINV medications

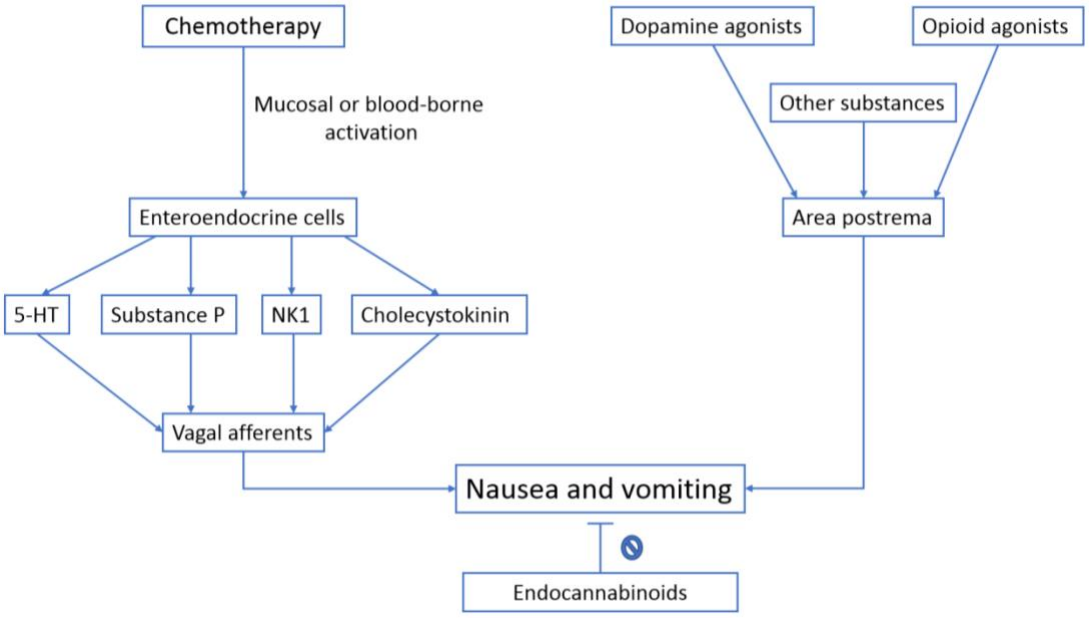


- The best treatment of CINV is to prevent it upfront with appropriate prophylactic medications
- Sometimes dyspepsia can be confused for CINV
- CINV prophylactic regimen should be tailored for:
  - The emetogenicity of the chemotherapy agents being administered
  - The patient's history with CINV
  - Patient-specific risk factors
- If a patient had prior CINV despite appropriate prophylactic medications, consider:

Strategies now	For future cycles
• Add additional breakthrough CINV medications • Schedule breakthrough CINV medications until better controlled • Optimize non-pharmacological therapies	• Escalate prophylactic regimen with next cycle (ex: move from moderate emetogenicity to high emetogenicity prophylactic regimen) • Add additional prophylactic CINV medications prior to the next chemotherapy cycle

Pathophysiology

- Studies suggest 2 major pathways that contribute to CINV:
  - Abdominal vagal afferents
  - Area postrema in the brain
- Chemotherapy acts primarily through the abdominal vagal afferents by stimulating enteroendocrine cells to release 5-hydroxytryptamine (5HT), substance P, neurokinin-1 (NK1), and cholecystokinin to induce acute CINV
- Area postrema appears to be activated by opioids and dopaminergic agonists to induce NV, but further study is needed



Risk factors

- Patients with the following risk factors are at higher risk for CINV:
  - Female
  - Younger age
  - History of motion sickness
  - Nausea during pregnancy
  - Higher emetogenicity of chemotherapy regimen
- Chronic alcohol use decreases CINV risk

Emetogenicity of chemotherapy agents

- Emetogenicity risk is determined by rate of CINV determined by the package insert or clinical trial
- In combination chemotherapy, emetogenicity rate is determined by the medication with the highest emetogenicity risk within the combination regimen
- Emetogenicity risk determines the prophylactic CINV regimens used prior to chemotherapy

Emetogenicity risk for intravenous chemotherapy

Emetogenicity risk (% emesis)	Chemotherapy agents/regimens		
High (> 90% emesis)	• AC (any anthracycline & cyclophosphamide) • Carboplatin AUC ≥ 4 • Carmustine (> 250 mg/m2)	• Cisplatin • Cyclophosphamide (> 1,000 mg/m2) • Dacarbazine • Doxorubicin (≥ 60 mg/m2)	• Epirubicin (> 90 mg/m2) • Ifosfamide (≥ 2G/m2/dose) • Mechlorethamine • Streptozocin
Moderate (> 30% - 90% emesis)	• Aldesleukin (> 12 – 15 mIU/m2) • Amifostine (> 300 mg/m2) • Arsenic trioxide • Azacitadine • Bendamustine	• Cytarabine (> 200 mg/m2) • Dactinomycin • Daunorubicin • Liposomal cytarabine and daunrorubicin • Dinutuximab	• Idarubicin • Ifosfamide (< 2G/m2/dose) • Interferon alfa (≥ 10 mIU/m2) • Irinotecan • Melphalan

	• Busulfan • Carboplatin AUC < 4 • Carmustine (≤ 250 mg/m2) • Clofarabine • Cyclophosphamide (≤ 1500 mg/m2)	• Doxorubicin (< 60 mg/m2) • Epirubicin (≤ 90 mg/m2)	• Methotrexate (≥ 250 mg/m2) • Oxaliplatin • Temozolomide • Trabextedin
Low (10% - 30% emesis)	• Ado-trastuzumab emtansine • Aldesleukin (≤ 12 mIU/m2) • Atezoliizumab • Belinostat • Blinatumomab • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Cytarabine (100 – 200 mg/m2) • Docetaxel • Doxorubicin liposomal	• Erbulin • Etoposide • 5-Fluorouracil • Gloxuridine • Gemcitabine • Intererfon alfa (5 – 10 mIU/m2) • Irinotecan liposomal • Ixabepilone • Methotrexate (50 – 250 mg/m2) • Mitimycin • Mitoxantrone • Necitumumab	• Olaratumumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin bound • Pemetrexed • Pentostatin • Pralatrexate • Romidepsin • Talimogene laherparepvec • Thiotepa • Topotecan • Ziv-aflibercept
Minimal (< 10% emesis)	• Alemtuzumab • Avelumab • Asparaginase • Bevacizumab • Bleomycin • Bortezomib • Cetuximab • Cladribine • Cytarabine (< 100 mg/m2) • Daratumumab • Decitabine • Denileukin diftitox • Dexrazoxane • Durvalumab	• Elotuzumab • Fludarabine • Interferon alpha (≤ 5 mIU/m2) • Ipilimumab • Methotrexate (≤ 50 mg/m2) • Nelarabine • Nivolumab • Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Pembrolizumab	• Pertuzumab • Ramucirumab • Rituximab • Rituximab/ Hyaluronidase SQ • Siltuximab • Temsirolimus • Trastuzumab • Valrubicin • Vinblastine • Vincristine • Vincristine liposomal • Vinorelbine

Emetogenicity of oral chemotherapy

Emetogenicity risk (% emesis)	Chemotherapy agents/regimens		
Moderate to high (≥ 30% emesis)	• Altretamine • Busulfan (≥ 4 mg/day) • Ceritinib • Crizotinib • Cyclophosphamide (≥ 100 mg/m2/day) • Enasidenib	• Estramustine • Etoposide • Lenvatinib • Lomustine (single day) • Midostaurin • Mitotane • Niraparib	• Olaparib • Panobinostat • Procabazine • Rucaparib • Temozolomide (> 75 mg/m2/day) • Trifluridine/tipiracil
Minimal to low (< 30% emesis)	• Abemaciclib • Afatinib • Alectinib • Axitinib	• Fludarabine • Gefitinib • Hydroxyurea • Ibrutinib	• Regorafenib • Ribociclib • Ruxolitinib • Sonidegib

- Bexarotene
- Brigantinib
- Bosutinib
- Busulfan (< 4 mg/day)
- Cabozantinib
- Capecitabine
- Chlorambucil
- Cobimetinib
- Cyclophosphamide (< 100 mg/m2/day)
- Dasatinib
- Dabrafenib
- Erlotinib
- Everolimus
- Idelalisib
- Imatinib
- Ixazomib
- Lapatiib
- Lenalidomide
- Melphalan
- Mercaptopurine
- Methotrexate
- Nilotinib
- Neratinib
- Osimertinib
- Palbociclib
- Pazopanib
- Pomalidomide
- Ponatinib
- Sorafenib
- Sunitinib
- Temozolomide (≤ 75 mg/m2/day)
- Thalidomide
- Thioguanine
- Topotecan
- Trametinib
- Tretinoin
- Vandetanib
- Vemurafenib
- Venetoclax
- Vismodegib
- Vorinostat

Pharmacological CINV interventions (Antiemesis NCCN Guidelines, Version 2.2022; JCO 2017;35:3240; Lexicomp)

5HT-3 antagonists

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Ondansetron	Acute	Y	Y	Y - ODT	• Headache (esp with IV) • Constipation • QTC prolongation (with other QTC prolonging medications) – exception is palonosetron	• Palonosetron is a long-acting 5HT-3 antagonist with effects lasting 3-7d. • Other 5HT-3 antagonists should not be given in combination with palonosetron to prevent additive side effects • Ensure adequate bowel regimen • Palonosetron doesn't prolong QTC
Palonosetron		Y	N	N		
Granisetron		Y	Y	Y - patch		
Dolasetron		Y	Y	N		

NK1 antagonists

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Fosaprepitant	Acute, delayed	Y	N	N	• Hypersensitivity reactions (only IV fosaprepitant) • Fatigue	• IV fosaprepitant contains polysorbate 80, a common hypersensitivity agent. If a patient has a reaction to IV fosaprepitant, they may be able to tolerate PO aprepitant which does not contain polysorbate 80 • No data for use after chemo (only as ppx) • PO aprepitant should be given as a 3d course • NK1 antagonists can inhibit dexamethasone metabolism and ↑ dex concentrations (except rolapitant)
Aprepitant		N	Y	N		
Rolapitant		Y	Y	N		

NK1 antagonists/5HT-3 antagonist combination

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Netupitant/ palonosetron	Acute, delayed	N	Y	N	• Headache • Fatigue • Constipation	• No data for use after chemo (only as ppx)

Atypical antipsychotics

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Olanzapine	Acute, delayed	N	Y	Y – ODT, IM* (IM reserved for psych)	• Fatigue • Drowsiness • EPS • LFT abnormalities • Orthostatic hypotension • Increased appetite	• Works best if scheduled • Consider lower doses of olanzapine in elderly or fragile patient (ex: use of olanzapine 5 mg daily to start) • CINV studies usually utilized olanzapine doses between 5 – 10 mg daily • May be an option for patients also having anxiety surrounding CINV or chemotherapy

Benzodiazepines

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Lorazepam	Acute, anticipatory, breakthrough	Y	Y	Y – rectal (reserved for seizures)	• Sedation • Disorientation • EPS • Respiratory depression • CNS depression	• Caution in hepatic and/or renal dysfunction • May be an option for patients with anxiety surrounding CINV or chemotherapy • Caution in the elderly • Very short half-life • Oral lorazepam can be placed buccally or sublingually for quick absorption if unable to swallow

Cannabinoids

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Dronabinol	Breakthrough	N	Y	N	• Dysphoria/ euphoria • Drowsiness/ sedation • Increased appetite	• May be an option for patients that use marijuana • Be cautious in patients with prior psychiatric or depression history • If initiating cannabinoids, start low and titrate up

Nabilone		N	Y	N	• GI symptoms • Hypotension • CNS symptoms • Tachycardia	• Use with caution in elderly patients and those with cardiac disorders • Dronabinol has been associated with seizures/seizure-like activity, monitor patients with seizure history closely

Phenothiazines

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Prochlorperazine	Acute, delayed, breakthrough	Y	Y	N	• EPS • Hypotension • Agitation • Dermatitis • Sleep disturbances • Urinary retention	• Both agents can cause anti-cholinergic side effects • Promethazine should not be administered SQ • Promethazine injection can cause severe tissue injury regardless of the route of administration • Promethazine is a vesicant • Promethazine is more sedating than prochlorperazine (due to more histamine blockade)
Promethazine		Y	Y	Y – suppository		

Steroids

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Dexamethasone	Acute, delayed, breakthrough, refractory	Y	Y	N	• Increased risk for GI bleed • Insomnia • Increased blood glucose • Increased risk for infections • CNS symptoms • Edema	• Certain chemotherapy regimens/clinical trials/cellular therapies might preclude the use of steroids • Steroid use for CINV alone is often short-term

Other

Medication	CINV type treated	IV	PO	Other forms	Side effects	Clinical pearls
Metoclopramide	Breakthrough	Y	Y	Y - ODT	• Drowsiness • Dystonic reactions • Restlessness • Urinary issues • EPS • Increased GI motility • CNS depression	• Avoid in patients with diarrhea, intestinal/bowel obstruction, bowel perforation, and/or GI bleed • Usually use of metoclopramide for CINV is short term.

Scopolamine	Breakthrough – motion related	Y – not for CINV	N	Y - patch	• Dysuria • Hypotension • Tachycardia • Dry mucosal membranes	• Effective with CINV related to motion or positional changes • Watch anti-cholinergic effects
Haloperidol	Acute, delayed, breakthrough	Y	Y	N	• Drowsiness • EPS • Headache • Hypotension • QTC prolongation (esp with IV) • CNS depression • Anti-cholinergic	• Caution with olanzapine, phenothiazines, and/or metoclopramide (can cause increased dopamine blockade → increased risk EPS) • Haloperidol has CINV effect at lower doses than what is used for psychiatric indications • Caution in elderly

Non-pharmacological CINV interventions

- Wear loose, comfortable clothing
- Stay in cool area, use small fan on face if needed
- Avoid strong smells
- Minimize strong, spicy foods
- Consider eating small meals throughout the day instead of large meals TID
- Relaxation techniques
- Acupuncture, acupressure
- Yoga

Prophylactic regimens

Out of scope for what you will be asked to do as a resident and typically built into chemotherapy orders input by oncology attendings / onc pharmacy. Can refer to **Antiemesis NCCN Guidelines, Version 2.2022** for further information).

Delayed, breakthrough and refractory CINV

- General treatment principles:
    - Add an agent from a different drug class
    - Scheduling CINV medications, especially prior to meals and pill administrations, can be effective in preventing and decreasing CINV
        - Remember to change medications to PRN when CINV is better controlled
    - Consider non-pharmacological interventions to decrease CINV
    - Rotate CINV medications as needed to see which agent works best for each patient
    - Evaluate and minimize any CINV triggers for the patient
- For future cycles, consider escalating prophylactic CINV medications
- Delayed and refractory CINV can be particularly difficult to treat and can lead to anticipatory CINV with future chemotherapy cycles if left uncontrolled

Anticipatory CINV

- Prevention of CINV with adequate prophylactic CINV regimens is a key factor in decreasing anticipatory CINV
- Behavioral therapy indicated to calm the patient can be helpful
- Non-pharmacological CINV interventions as mentioned above can be helpful
- Consider anxiolytic therapies to decrease anticipatory CINV (see benzodiazepines)

Overview

- Breast cancer is the most common cancer in women, 2nd leading cause of cancer-related deaths in the USA
- Risk factors include older age, early menarche, late menopause, late age at 1st pregnancy/nulliparity, benign proliferative lesions w/ typia, dense breast tissue, family hx of breast CA in 1st degree relatives, alcohol, previous chest radiation (e.g. for Hodgkin lymphoma), germline mutations (such as BRCA 1/2, PALB2), and possibly post-menopausal hormone replacement therapy (**NEJM 2006;354:270**) (but *no increased breast cancer risk w/ low-dose combined oral contraceptives* ***NEJM 2002;346:2025***)

Screening

Varying guidelines depending on organization

- Age 40+ vs 50-74, q1-2 years
- Mammogram +/- clinical exam +/- self exam (mammogram optimal benefit is age 50+)

Annual breast MRI *in addition to* mammogram: for high-risk patients (BRCA, other genetic syndromes, 1st degree BRCA in family if patient's BRCA status unknown, history of chest irradiation 10-30 yo, strong family history w/ an elevated lifetime risk of breast CA based on risk models)

Genetics

- Hereditary Breast Cancer Mutations: BRCA 1/2, PTEN, TP53, ATM, PALB2
- For genetic high-risk patients, bilateral mastectomy reduces breast cancer risk by 90% (**Breast Cancer Res Treat 2011;125:837**), but evidence suggests annual screening w/ mammoraphy and MRI has the same benefit.

Pathological Subtypes

The two most common types of breast cancer are ductal carcinoma and lobular carcinoma. Each type can be invasive (involving the stroma) or non-invasive / in situ (confined to ducts / lobules). Of note, the **status of ER / PR / HER2 positivity (discussed below) and not histology is what drives Tx.**

- **Ductal carcinoma:**
  - Ductal carcinoma in situ (DCIS) – Cancer confined to the duct
  - Infiltrating ductal carcinoma – Most common. 70-80% of invasive disease
- **Lobular carcinoma:**
  - Lobular carcinoma in situ (LCIS) – Not considered malignant but risk factor for developing invasive disease in the future
  - Invasive lobular – 2nd most common. 5-10% of invasive disease. More likely to be bilateral, multicentric and w/ better prognosis than ductal carcinoma. Generally, ER+ and occur in older women. A/w mutation in cadherin (CDH1)
- Other, less common types: Inflammatory (faster-growing, 1-5% of breast cancers), mucinous (colloid), tubular, medullary, papillary, metaplastic, invasive micropapillary

Breast Cancer Molecular Subtypes

Breast cancer is prognostically/therapeutically classified by **receptor status**:

1. Hormone Receptor Positive (HR+): ER+ and/or PR+, HER2-
2. HER2 Positive (HER2+): HER2+, regardless of ER/PR status
3. Triple Negative: ER-/PR-/HER2-

- **Estrogen Receptor (ER+):** ER+ breast cancer is the most common type of breast cancer and has the best prognosis. However, recurrences may occur even after 5 years (delayed recurrence). Patients w/ ER+ breast cancer typically undergo surgery and receive endocrine therapy, alone or in combination. For patients w/ early stage breast cancer, OncotypeDx risk recurrence scores *(see below)* can help direct Tx decisions regarding risk/benefit of adjuvant chemotherapy.
- ER+ breast cancer is especially implicated in late recurrence. If a patient has a history of ER+ breast cancer, however distant, recurrence risk is significant.

- **Progesterone Receptor (PR+):** PR expression is linked to the pathophysiology of the estrogen receptor (**Expert Rev Endocrinol Metab 2011;6:359**). Like ER+ disease, PR+ breast cancer is more likely to respond to hormone therapy. Co-expression of ER and PR correlates w/ an even higher response rate to endocrine therapy.

- **HER2/Neu (HER2+):** HER2 is an oncogene amplified in certain types of breast cancer. Amplification is determined by fluorescent in situ hybridization (FISH) and/or immunohistochemistry (IHC), and it implicates more aggressive disease. Fortunately, these tumors respond very well to targeted HER2 therapies *(see below)*.

- **Triple-Negative:** These cancers do not express ER or PR and they do not have HER2/neu amplification. Unfortunately, there are no FDA-approved targeted therapies for this type of breast cancer and management is primarily restricted to chemotherapy.

Genomic Profiling

- Oncotype Dx is a genetic test used to determine whether certain patients would benefit from chemotherapy. This test is validated for patients w/ early-stage, ER+/HER2- disease. It measures 21 genes (16 cancer-related, 5 reference genes) to calculate a *risk recurrence score* (**Breast Cancer Res Treat 2017;165:65**). This score helps physicians determine the likelihood of distant recurrence and potential additive benefit of adjuvant chemotherapy to endocrine therapy.
- SNaPshot is an MGH-developed genomic test for molecular profiling of tissue biopsies. The majority of metastatic solid tumor patients at MGH undergo SNaPshot to identify potential actionable mutations for targeted therapy selection (usually via clinical trials).

Staging Overview

- Tumor, Node, Metastasis (TNM) System: T: tumor size and extension, N: regional/distant lymph node involvement, M: distant metastases designation.
- Helpful Classifications: **Early Stage:** Stage I, IIA, IIB (if T2N1), **Locally advanced:** Stage IIB (if T3N0), IIIA, IIIC, **Stage IV**: M1 w/ any T, N.
- Staging AJCC 8th edition (**Ann Surg Oncol 2018;25:1783**):

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)	Ductal carcinoma in situ
Tis (Paget)	Paget disease not associated with invasive carcinoma or DCIS
T1	Tumor size ≤ 20 mm
T1mi	Tumor size ≤ 1 mm
T1a	Tumor size > 1 mm but ≤ 5 mm
T1b	Tumor size > 5 mm but ≤ 10 mm
T1c	Tumor size > 10 mm but ≤ 20 mm
T2	Tumor size > 20 mm but ≤ 50 mm
T3	Tumor size > 50 mm
T4	Tumor with direct extension to the chest wall and/or the skin with macroscopic changes
T4a	Tumor with chest wall invasion
T4b	Tumor with macroscopic skin changes including ulceration and/or satellite skin nodules and/or edema
T4c	Tumor with criteria of both T4a and T4b
T4d	Inflammatory carcinoma

Stage	TNM
Stage 0	Tis, N0, M0
Stage IA	T1, N0, M0
Stage IB	T0, N1mi, M0 T1, N1mi, M0
Stage IIA	T0, N1, M0 T1, N1, M0 T2, N0, M0
Stage IIB	T2, N1, M0 T3, N0, M0
Stage IIIA	T0, N2, M0 T1, N2, M0 T2, N2, M0 T3, N1, M0 T3, N2, M0
Stage IIIB	T4, N0, M0 T4, N1, M0 T4, N2, M0
Stage IIIC	Any T, N3, M0
Stage IV	Any T, Any N, M1

Treatment

- Local Management: For non-metastatic disease, options typically include **breast conserving therapy vs. mastectomy**, which have similar local control and OS in multiple clinical trials, assuming appropriateness and feasibility of BCT (see below).
  - Breast Conserving Therapy: Involves **lumpectomy (removal of tumor only w/ goal of negative margins), usually followed by whole breast RT**. XRT may be omitted in women ≥65 yo w/ small tumors (<3cm) that are HR+, HER2- (**Cancer 2013;119:1402**)
  - Modified Radical Mastectomy: Radical mastectomy was historically a morbid procedure. Today, patients typically undergo ***modified* radical mastectomy** (removal of breast while sparing pectoralis major), which is less aggressive w/ similar outcomes.
    - Indications for mastectomy:
      - 2+ primary tumors in different quadrants (multicentric)
      - Widespread microcalcifications
      - Significant prior chest radiation
      - Positive margins after breast conserving surgery
      - Large tumor not appropriately shrunk by neoadjuvant therapy
      - Prophylaxis (see genetic high-risk patients above)

Indications for post-mastectomy chest wall radiation:
- 4+ lymph nodes
- Tumor >5 cm
- Stage III disease
- Positive surgical recurrence

- Lymph Node Evaluation: LN positivity is an important prognostic factor. **Sentinel lymph node (SLN) Bx to sample a limited number of the closest nodes where cancer is most likely spread first is appropriate and standard now for axillary staging of early stage BCa w/ clinically negative LNs on exam**. More extensive axillary lymph node dissection (ALND) may be required though if multiple SLN (+), if clinical axillary exam reveals LN+ disease, or if tumor is locally advanced / inflammatory BCa (high-risk for spread).

- Medical Management of Breast Cancer:
  - ***Hormone Receptor+ Breast Cancer:***
    - Endocrine Therapy:
      - Premenopausal/Peri-menopausal: **Tamoxifen**, an oral selective **estrogen receptor modulator (SERM)** whose metabolites compete w/ estrogen to bind w/ ER. Tamoxifen for 5-10 yrs is recommended in all low-risk, pre-menopausal, HR+ pts. High-risk pts (≤35 yo, requiring adjuvant chemo) may benefit from **ovarian suppression w/ GnRH agonist OR oophorectomy + SERM/aromatase inhibitor**
      - Postmenopausal: An **aromatase inhibitor** (AI; **anastrazole, letrozole, exemestane**) is typically used. Inhibits peripheral conversion of circulating steroidal precursors to estrogen and is superior to Tamoxifen. However**,** Tamoxifen is acceptable if intolerant to AI

    If aromatase is inhibited in *premenopausal* women, the ovaries will produce even more estrogen in compensation.

    - Adjuvant Chemotherapy: Generally recommended for triple-negative and HER2+ tumors, as well as select HR+ tumors (for HR+, consider sending Oncotype Dx *(see above)* to determine recurrence risk score and subsequent need for chemotherapy after surgery)
    - Metastatic Disease:
      - Hormone therapy: SERM (e.g. oral Tamoxifen), selective estrogen receptor degrader (SERD, e.g. IM fulvestrant), or oral AI
      - CDK 4/6 Inhibitors (oral): Ribociclib, Palbociclib, Abemaciclib (in conjunction w/ AI)
      - PIK3CA inhibitor (oral): Alpelisib (in conjunction w/ fulvestrant if PIK3CA-mutated)
      - mTOR inhibitors (oral): Everolimus
      - Chemotherapy: multiple options
  - ***HER2+ Breast Cancer (targeted therapies):***
    - Trastuzumab (IV and SQ): HER2/neu receptor inhibitor which binds to extracellular domain of receptor **first line in neoadjuvant setting* (Lancet Oncol 2013;14:461)
    - Pertuzumab (IV): HER2 dimerization inhibitor that is combined w/ trastuzumab (since different mechanism) and docetaxel for neoadjuvant or metastatic therapy
    - Lapatinib (PO): tyrosine kinase inhibitor targeting HER2 and EGFR
    - Neratinib (PO): Irreversible pan-HER tyrosine kinase inhibitor
    - Trastuzumab emtansine (T-DM1, IV): antibody-drug conjugate of trastuzumab and the tubulin binding emtansine. **EMILIA trial: T-DM1 improved survival in metastatic HER2+ patients resistant to trastuzumab alone, w/out a significant risk of serious toxicity (Lancet Oncol 2017;18:732, NEJM 2012;367:1783)*
  - ***Triple Negative Breast Cancer:***
    - Unfortunately, these cancers do not typically respond to hormonal or targeted therapy
    - Tx backbone is typically chemotherapy
  - ***BRCA mutant Breast Cancer:***
    - *BRCA 1/2 mutation*: Increases risk of breast (HR+ and/or TNBC), ovarian, and pancreatic cancer.
    - Sensitive to DNA-damaging agents and PARP inhibitors

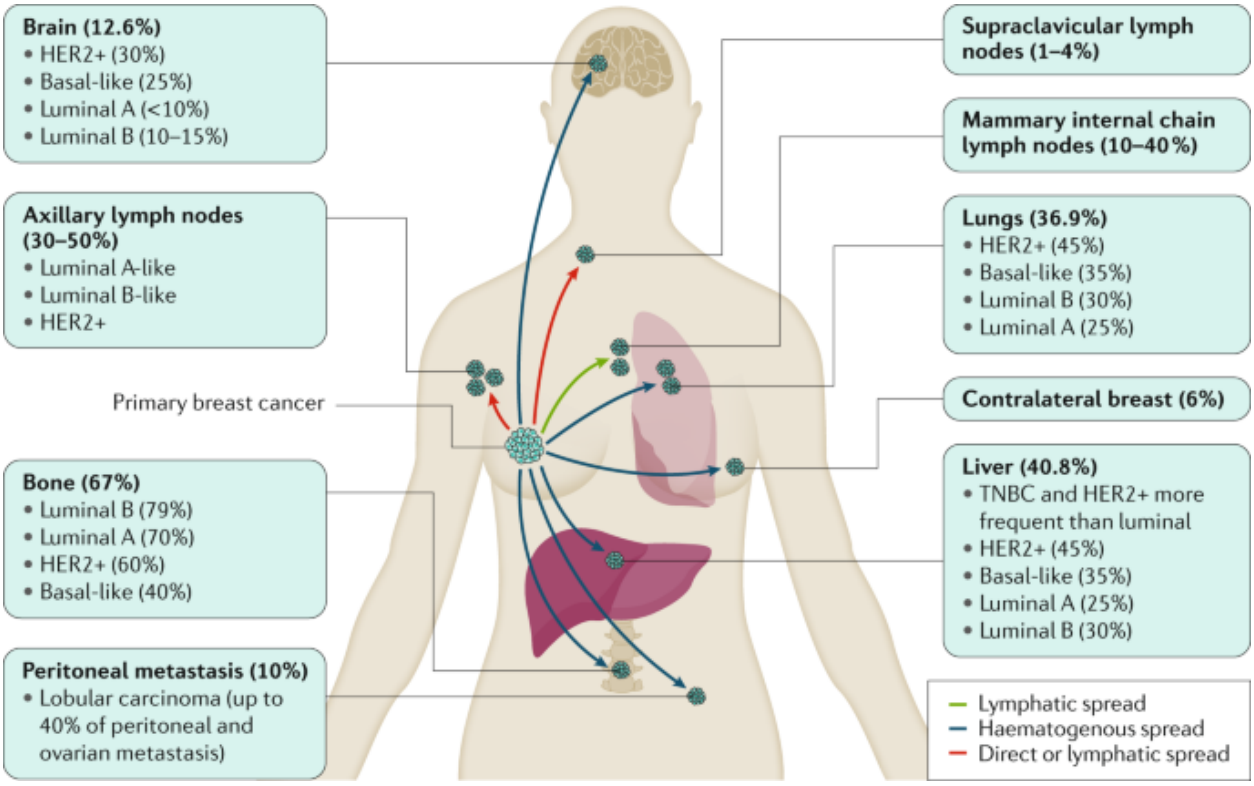
Treatment of Metastatic Breast Cancer:

Treatment	Monitoring Response/Progression
Chemotherapy: (multiple options)	Imaging: Restaging scans *every 2-3 months*. ▪ **CT Chest/Abdomen/Pelvis**: most commonly used ▪ **Bone scans**: coupled w/ CT C/A/P every 2-3 months if ER+ disease or bony disease. ▪ **PET/CT**: could replace CT chest/abdomen/pelvis *and* bone scans. If a patient has **stable** disease, the restaging interval may be increased. ▪ **Brain MRI**: metastatic HER2+ and TNBC associated w/ brain mets and could **consider** MRI (recommended over CT), particularly if there are neurologic symptoms.
Targeted Therapy: ▪ ER/PR+: CDK 4/6 Inhibitors (palbociclib, ribociclib, abemaciclib); mTOR inhibitors (everolimus) ▪ HER2 inhibitors: see *targeted therapy above*	
Hormone Therapy: ▪ ER/PR+: see *hormone therapy above*	Tumor Markers: **CE**, **CA15-3**, **CA 27.79** - sent only in the metastatic setting. Monitoring levels of these tumor markers serves as a surrogate marker for response and progression.

Major Side Effects of Breast Cancer Medications (For general chemotherapy SE, see "Solid Tumor Oncology: Introduction"):

Drug	Side Effect
Tamoxifen	hot flashes, sexual dysfunction, DVT, endometrial cancer
Raloxifene	DVT (no risk of endometrial Ca since it is antagonist rather than agonist in uterus)
Aromatase inhibitors	Hot flashes, sexual dysfunction, osteoporosis/fractures, CV disease, MSK syndrome
Trastuzumab	Reversible heart failure via LV injury (patients should get TTE prior to treatment initiation and during Tx)
Trastuzumab emtansine	HFrEF, thrombocytopenia, liver toxicity
Pertuzumab	Diarrhea, rash
Lapatinib	milder symptoms typically (GI upset common)
CDK 4/6 inhibitors	Neutropenia
mTOR inhibitors	Rash, mucositis, thrombocytopenia
PIK3CA inhibitor	hyperglycemia, rash, diarrhea
PARP inhibitors	Myelosuppression

Common metastatic sites from Harbeck et al. 2019 (Nat Rev Dis Primers 2019;5:66):



*Note: **Brain metastases** from breast cancer are typically ***not*** **hemorrhagic**. OK to use anticoagulation when needed.

Esophageal Cancer

Two major pathologic types: Squamous cell (SCC) and Adenocarcinoma (Adeno)

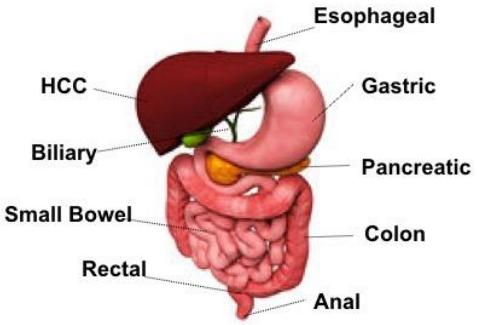
Risk Factors:

- Squamous: Smoking, alcohol
- Adeno: GERD, Barrett's w/ intestinal metaplasia, obesity, and smoking

Symptoms: progressive dysphagia (solid → liquid), odynophagia, wt loss, GIB

Initial Staging:

- EUS important for locoregional staging; invasion depth; evaluation of thoracic and hepatogastric lymph nodes, liver mets, & malignant ascites.
- PET-CT – eval for LAD and metastatic dz.



Types of cancers affecting the GI system

General Principles of Management:

- Stage I (early disease)
  - Clinical T1N0 - local tx w/ endoscopic resection, ablation, or esophagectomy.
- Stage II, III (locoregional)
  - Clinical T2N0 SCC- initial resection if <2 cm and well differentiated
  - Clinical T2N0 Adeno- upfront chemoRT for distal esophagus and EGJ
  - Clinical T3-T4 or N+ locoregional dz pre-operative neoadjuvant tx w/ chemo/RT followed by esophagectomy improves survival in pts w/ potentially curable esoph CA (CROSS trial, Lancet Oncol;16:1090)
    - First-line chemo: FOLFOX vs ECF (epirubicin, cisplatin, 5FU) vs Taxane-based regimen
- Stage IV-B (advanced, metastatic)
  - 1st line Pembrolizumab plus chemo (platinum & fluoropyrimidine-based) for previously untreated advanced/unresectable or metastatic esoph Adeno or SCC, or GEJ Adeno (KEYNOTE-590, Lancet 2021;398:759)
  - Palliative chemo (see Gastric Cancer section below)
- Residual pathologic dz
  - s/p neoadjuvant chemo/RT for esophageal or EGJ cancer (SCC or Adeno) w/ residual pathologic dz following surgery benefit from nivolumab therapy for up to 12 mo. Tx w/ nivolumab doubles median dz-free survival regardless of histology, location, staging, and PD-L1 status (CheckMate 577, NEJM 2021;384:1191)

Gastric Cancer

Types: Gastric adenocarcinoma (>90%), lymphoma (MALT), sarcoma (GIST), carcinoid

Risk factors: obesity, tobacco, EtOH, H pylori, pernicious anemia, EBV, high salt and N-nitroso enriched diets, genetic predisposition and hereditary syndromes

Symptoms: early satiety, wt loss, persistent abdominal pain (epigastric), dysphagia (proximal stomach), GIB, palpable abdominal mass, LAD, ascites, rarely paraneoplastic (diffuse seborrheic keratoses→ sign of Leser-Trélat).

Four major molecular subtypes of gastric adenocarcinoma (Nature 2014;513:202):

- Tumor classification system by pathologic subtypes
  - Intestinal: tubular/glandular formation of tumor cells
  - Signet ring: diffuse type, lack of glandular formation, poor prognostic factor
- Classification system based on molecular profiling, (The Cancer Genome Atlas (TCGA) Research Network) includes:
  1. EBV+ tumors that show recurrent PIK3CA mutations, DNA promoter hypermethylation, amplif of JAK2, PD-L1/L2
  2. Microsatellite-unstable tumors that show elevated mutation rates (important for immunotherapy considerations)
  3. Genomically-stable tumors which are enriched in diffuse histological variant and mutations in RHO-family genes
  4. Chromosomally-unstable tumors which are enriched in intestinal histological variant and show marked aneuploidy, TP53 mutations, amplification of receptor tyrosine kinases

Initial Staging:

- CT Chest, abdomen, and pelvis
- PET-CT – eval for LAD and metastatic dz
- EUS – eval for depth of invasion and biopsy
- Laparoscopy- for evaluation of occult metastatic and peritoneal dz

General Principles of Management (Gastric Adenocarcinoma):

- Stage I-III (locoregional)
  - Subtotal gastrectomy can be curative (goal: complete resection margins >4cm). Standard of care is dissection of all group 1 and group 2 nodes (D2)

- Perioperative vs neoadjuvant +/- RT pending extent of dz
  - FLOT (5FU, Leucovorin, Oxaliplatin, Docetaxel) is new standard of care for peri-operative tx (Lancet Oncol 2016;17:1697). In practice, FOLFOX often still used. Sometimes FOLFIRINOX.
- Stage IV (advanced)
  - Chemo-based regimens using either 5FU, taxol, irinotecan or platinum-based therapies
  - Targeted therapy
    - HER2- advanced/unresectable or metastatic gastric, EGJ, or esophageal adeno: Tx w/ Nivolumab combined w/ a fluoropyrimidine and platinum-containing regimen for initial tx (CheckMate 649, Lancet 2021;398:27) for pts w/ CPS ≥5 or MMRd.
    - ~20% gastric CAs overexpress HER2, ToGA trial (Lancet 2010;376:687) → FDA approval of Trastuzumab in HER2+ metastatic gastric pts; given w/ chemo capecitabine/cisplatin/FOLFOX
    - HER2+/overexpressing locally advanced, metastatic gastric, EGJ adeno: Tx w/ pembrolizumab, trastuzumab and fluoropyrimidine plus platinum-containing chemo (KEYNOTE-811, Nature 2021;600:727).
    - VEGFR-2 also involved in gastric CA pathogenesis. Rainbow trial (Lancet Oncol 2014;15:1224) showed ↑ survival w/ ramucirumab (monocloncal VEGFR-2 antagonist) + paclitaxel. Usually 2nd line or beyond.

Pancreatic Cancer

Two major pathologic types:

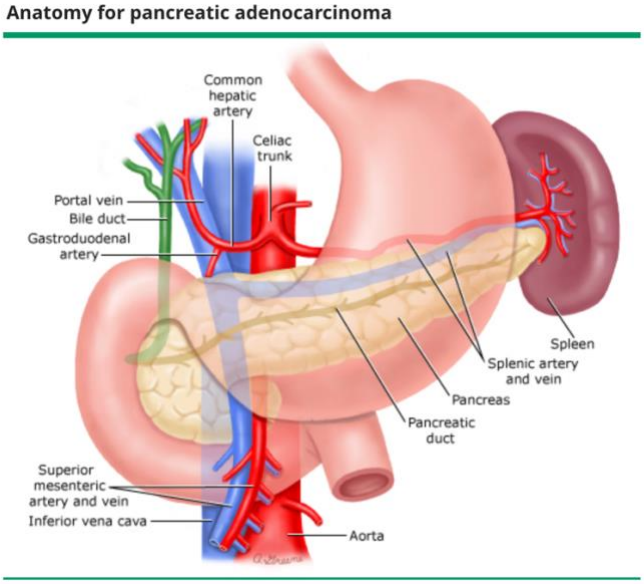
- PDAC (pancreatic ductal adenocarcinoma): originate from ductal epithelial cells (>90% of pancreatic CAs)
- pNET (pancreatic neuroendocrine tumor): originate from hormone-producing cells

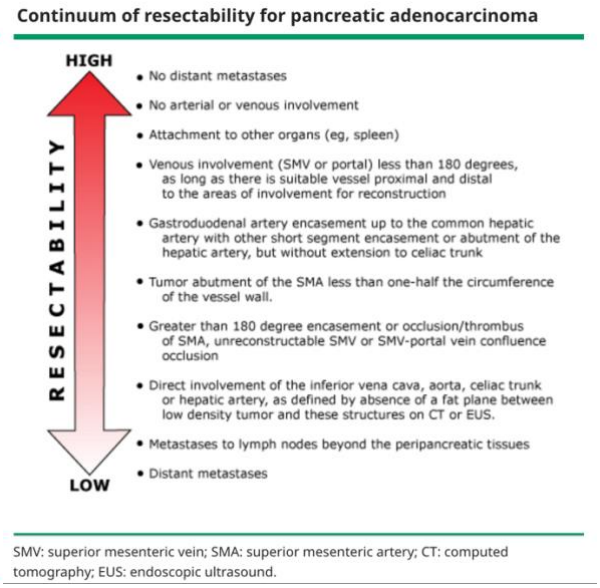
Risk factors: age, chronic pancreatitis, obesity, smoking, EtOH, DM, exposure to certain chemicals, genetic syndromes (BRCA1/2, PALB2, p16/CDKN2A, PRSS1, MLH1/MSH2, STK11)

Symptoms: abd pain, back pain, weight loss, cachexia/anorexia, painless jaundice, biliary colic, pruritis

Objective Findings: painless jaundice + palpable gallbladder (Courvoisier sign), ascites (intra-abdominal dz), HSM (2/2 liver mets, portal vein obstruction), paraumbilical LAD (Sister Mary Joseph nodule: subQ mets), left supraclavicular nodule (Virchow's node), worsening hyperglycemia/DM, new DVT/migratory thrombophlebitis (Trousseau syndrome)

Pancreatic Cancer Staging (TNM rarely used, resectability is most important, NCCN Guidelines v1.2022)





Medical Complications:

- DM, cholangitis, SBO (partial vs complete), biliary obstruction, gastric outlet obstruction, abdominal pain (can radiate to the back at times), malabsorption (loss of fat-soluble vitamins), diarrhea

Initial Workup:

- High-contrast CT ab/pelvis, chest CT, ERCP if biliary obstruction, EUS for biopsy, LFTs, CA19-9, PET/CT in high-risk pts, MRI if needed to assess indeterminate liver lesions, germline testing

General Principles of Management (**NEJM 2014;371:1039**):

- **Resectability** (~15-20% resectable w/ clear planes around critical vascular structures)
  - Resectable: (consider laparoscopy first) Surgery → adjuvant chemo w/ or w/out RT
  - Resectable but high-risk (based on imaging, significantly elevated CA 19-9, large primary, large regional LN, excessive wt loss, extreme pain): Neoadjuvant chemo (FOLFIRINOX, FOLFOX, gemcitabine + nabpaclitaxel) → RT → surgery
  - Borderline (abutment/limited involvement of vascular structures): Ongoing studies re: neoadjuvant tx converting borderline tumors to resectable ("conversion approach"), goal is neoadjuvant chemo (FOLFIRINOX, FOLFOX, gemcitabine + nabpaclitaxel) → RT → surgery → outback chemo depending on neoadjuvant course
  - Unresectable: Neoadjuvant chemo/RT w/ hopes of converting to resection
  - Metastatic disease: Assess performance status, germline or somatic mutation in a gene associated w/ HRR (homologous recombination repair) deficiency, comorbidity, serum bili level, and histology. Performance Status (PS) determines tx regimen.
    - PS 0-1 w/ favorable comorb profile: FOLFIRINOX or dose-modified FOLFIRINOX or gemcitabine plus nab-paclitaxel
    - PS 2: gemcitabine, gemcitabine plus capectabine, gemcitabine plus nab-paclitaxel, gemcitabine plus S-1
    - Poor PS (3+): Supportive care, chemo case-by-case.
- Surveillance following surgery:
  - CT chest/ab/pelvis Q3-6mo, CA-19-9
- Pts w/ BRCA1/2 mutations can transition to PARPi maintenance after 4-6mo systemic tx for metastatic dz.
- Pts w/ pathogenic alterations in homologous recombination repair genes (eg BRCA, PALB2) benefit more from platinum regimens (eg. FOLFIRINOX)

FOLFIRINOX: FOL = folinic acid (leucovorin), F = 5FU (fluorouracil), IRI = irinotecan, OX = oxaliplatin
FOLFOX: FOL = folinic acid (leucovorin), F = 5FU (fluorouracil), OX = oxaliplatin

Hepatocellular Carcinoma (HCC)

Risk factors: viral hepatitis (HBV, HCV) – accounts for 75% cases worldwide, cirrhosis (HBV, HCV, alcoholic, autoimmune, NASH, hemochromatosis,), environmental exposures (aflatoxin, EtOH, smoking), genetic (Hereditary hemochromatosis, Alpha-1 antitrypsin deficiency, Acute intermittent porphyria).

Screening: for pts at risk (known HBV, HCV, cirrhosis, porphyria), AFP w/ abdominal imaging (US, MRI) Q6-12mo

- Check **AASLD guidelines** for distinct pt populations and screening plan

Initial Workup:

- LFTs, AFP, CBC, INR, Albumin, **Child-Pugh Score** for Cirrhosis Mortality, Triple Phase CT or Liver MRI w/ HCC protocol
- Often HCC can be diagnosed radiographically, obviating the need for biopsy and pathologic confirmation. Radiographic criteria include arterial hypervascularity and venous or delayed phase washout (see **AASLD guidelines** for HCC dx criteria).

Liver Transplant Criteria (**NEJM 1996;334:693**, **NEJM 2001;33:1394**):

- Milan Criteria: 1 lesion ≤ 5cm -OR- 3 lesions ≤ 3cm each; No regional nodal, distant metastases or gross vascular invasion
- UCSF Criteria: single tumor ≤ 6.5cm -OR- 2-3 tumors w/ a total tumor diameter ≤ 8cm

General Principles of Management (HCC):

- Surgical Resection
  - <20% resectable due to complicating factors: cirrhosis w/ portal HTN, multifocal lesions, gross vascular invasion
- Liver Transplantation
  - Potentially curative for early stage HCC
  - Prior to transplant, other modalities can be used as bridge (RFA, TACE, External Beam Radiation)
  - Pts w/ HCC receive MELD exception points to account for increased waitlist mortality not reflected by their **MELD score**. Criteria include presence of 1 lesion between 2-5 cm or 2-3 lesions ≤ 3cm (Milan Criteria), provided no vascular invasion or extrahepatic dz.
- Locoregional Therapies
  - Goal to ↓ blood flow to tumor and/or deliver localized high doses of chemo or RT → tumor necrosis. Options include:
    1) Percutaneous ablation (radiofrequency ablation: RFA, or microwave ablation: MWA)
    2) Intra-arterial embolization (TACE: transcatheter arterial chemoembolization or radioembolization)
    3) External Beam Radiation
- Systemic Treatment
  - Atezolizumab plus bevacizumab for advanced unresectable HCC (**NEJM 2020;382:1894**) w/ ECOG 0-1, no worse than Child-Turcotte-Pugh class A cirrhosis, w/out recurrence after transplant, no AC, appropriate management of esophageal varices- better overall and progression-free survival than sorafenib

- Recurrence after liver transplantation or other contraindication to atezolizumab and bevacizumab- recommendation is sorafenib or lenvatinib.
  - Sorafenib (kinase inhibitor) improved median survival and time to progression by 3mo (**NEJM 2008;359:378**)
  - Lenvatinib (VEGFR antagonist) is non-inferior to Sorafenib (**Lancet 2018;391:1163**)
- Combo nivolumab + ipilimumab approved for tx of HCC in pts previously tx w/ sorafenib (**JAMA Onc 2020;6:e204564**)
- Subsequent line options include Regorafenib and Cabozantinib for Child-Pugh Class A and Ramucirumab for AFP ≥400, ipi/nivo, pembro, nivo

Colon Cancer

Risk factors:

- Age, hereditary colon CA syndromes (FAP – APC mutation, HNPCC/Lynch – DNA MMR mutations, Peutz-Jeghers – STK11 mutation, and others), personal/family history of CRC, adenomas, IBD (UC>CD), pelvic/abd RT, CF, black, male, acromegaly, renal transplant, obesity, DM, red/processed meat, tobacco, EtOH, androgen depriv. tx, cholecystectomy

Molecular Alterations in CRC:

- Progressive accumulation of genetic mutations or epigenetic alterations that activate oncogenes and inactivate tumor suppressor genes causing transformation over time from normal colonic epithelial cells → aberrant crypt foci → early adenoma → advanced adenoma → adenocarcinoma (usually takesy from adenoma to CA)
- Different sequences identified for adenoma → CA transformation (APC-driven) vs serrated polyp → CA (CpG island methylation phenotype (CIMP)-driven)

Screening: (See **Section 7.1** for further information for CRC screening guidelines)

- General population:
  - Visual exams: colonoscopy Q10y (alternative: CT colonography Q5y, flex sig Q5y, or flex sig Q10y + FIT Q1y)
  - Stool-based tests: fectal immunochemical test (FIT) Q1y, high sensitivity guaiac-based fecal occult blood test (HSgFOBT) Q1y, multi-targeted stool DNA test Q1 or 3y
- At-risk populations:
  - Personal history of polyps: time of re-testing depends on # and type of polyp (Gastroenterologist who performs the colo often helps inform when next colo should be done)
  - Family history: CRC in any first degree relative <60 yo or in 2 or more first-degree relatives at any age– start screening colos at age 40 or 10y before the youngest case (whichever earlier)
  - IBD: colo ≥8y after onset of symptoms, then Q1-3y w/ biopsies.
  - HNPCC/Lynch or FAP: start screening at age 20-25 or 5y before youngest case in family, then Q1-2y w/ biopsies; genetic testing should be offered to relatives.
  - FAP: start screening at age 10-12 w/ sigmoidoscopy or colo Q1-2y. Yearly colos once polyps are found until a colectomy is planned.

Presentation: Change in bowel habits, iron def, melena, hematochezia, obstruction, abdominal pain, Strep bovis or clostridium septicum bacteremia, weight loss, RUQ pain or LFT abnormalities if hepatic metastases

Initial Workup:

- Colo w/ bx, CT chest/ab/pelvis, CBC/BMP, CEA, molecular dx (microsatellite instability (MSI), mismatch repair (MMR))

General Principles of Management (Colon Cancer, **NCCN Guidelines v.1.2022**):

- Stage I (local dz) → definitive tx is surgery alone
- Stage II (node negative) → surgery +/- adjuvant chemo (more commonly not given unless high-risk clinical features, i.e. deeper invasion, higher grade, bowel obstruction)
- Stage III (node positive) → surgery followed by adjuvant chemo (e.g. FOLFOX or CAPEOX)
- Stage IV (metastatic dz) → generally evaluate for option of resection if limited metastatic dz or need for palliation of symptoms w/ integration of chemo; if asymptomatic tumors w/ unresectable mets, no surgery, rather chemo.
  - Chemo regimens include variations of: FOLFOX, CAPEOX, FOLFIRI, FOLFOXIRI. Can combine w/ bevacizumab or anti-EGFR therapies (if RAS-WT)
- Primary tumor location matters (right vs left)
- Other subtypes to consider: BRAF (poor prognosis), HER2, MSI
- Note that rectal CA tx is distinct from that for colon CA and often involves RT as well as the potential for neoadjuvant tx

FOLFOX: FOL = folinic acid (leucovorin), F = 5FU (fluorouracil), OX = oxaliplatin
CAPEOX: CAPE = capecitabine (oral pro-drug of 5FU), OX = oxaliplatin
FOLFIRI: FOL = folinic acid (leucovorin), F = 5FU (fluorouracil), IRI = irinotecan
FOLFOXIRI: FOL = folinic acid (leucovorin), F = 5FU (fluorouracil), OX = oxaliplatin, IRI = irinotecan

Overview (NCCN Guidelines for NSCLC v.2.2022, NCCN Guidelines for SCLC v.2.2022)

- Worldwide, 2.1 million patients in 2018 w/ 1.7 million deaths (CA Cancer J Clin 2018;68:394)
  - **15% is small cell lung cancer (SCLC)**
    - Often disseminated at diagnosis. Very chemoresponsive, but poor prognosis.
  - **85% is non-small cell lung cancer (NSCLC)**, of which lung adenocarcinoma (ADC) >> squamous cell (SCC) cancer
    - Heterogeneous group of diseases. Molecular characterization of tumor tissue key to guiding tx.
- Despite all advances, 84% of those diagnosed will die (deadliest in US). 85% of lung CA caused by smoking.
- Duration of smoking increases risk of lung CA more than number of cigarettes per day (1:33x vs 1:1x). Risk declines after 10-15y abstinence, but never to risk of non-smokers (half of lung CA occurs in former smokers)
- Smokers and non-smokers tend to have different molecular profiles (p53 and KRAS vs. EGFR and ALK fusions, respectively)

Screening

- The National Lung Screening Trial – randomized, multicenter trial comparing LD helical chest CT w/ CXR for screening >50K smokers (30+ PY; or quit w/in 15y) ages 55-74. 20% relative reduction in lung CA mortality (NEJM 2011;365:395)
- 2021 USPSTF recommends: **Annual** low-density CT for patients ages 50 to 80 w/ 20-pack/year or more, who are currently smoking, or quit w/in the past 15y. Screening should be discontinued once the individual has not smoked for 15y of has limited life expectancy (JAMA 2021;325:962)

Initial evaluation (NCCN Guidelines for NSCLC v.2.2022, NCCN Guidelines for SCLC v.2.2022)

- Symptoms - anorexia, fatigue, weakness, cough, SOB, foamy sputum, and low-grade fever; slightly less common hemoptysis and symptomatic brain mets
- Metastasis at diagnosis in 75% of SCLC and 50% adenocarcinoma mo lung (ips/contralat), brain, bone/marrow, liver, and adrenal glands being most common (JCO 2004;22:2865)
- Paraneoplastic syndromes in NSCLC include:
  - Hypercalcemia (due to bone metastasis >> PTHrP)
  - Hypertrophic osteoarthropathy (HOA): abnl skin, osseous proliferation of extremities; can also present as pain in large joint. More common than clubbing.
- Paraneoplastic syndromes in SCLC include:
  - Cushing syndrome caused by excessive corticotropin (ACTH) production. Can occur mo muscle weakness, weight loss, hypertension, hyperglycemia, and profound hypokalemia WITHOUT classical stigmata of Cushing's.
  - SIADH secretion frequently caused by SCLC and results in hyponatremia. Tx is focused on treating the malignancy (in majority of patients, hyponatremia will resolve w/in weeks of starting chemo.
  - CNS paraneoplastic disorders including cerebellar degeneration, dementia, limbic encephalopathy, Lambert-Eaton syndrome (<1%), and optic neuritis/retinopathy (all antibody mediated).
- Uncommon at presentation: hoarseness, SVC syndrome, tamponade, and paraneoplastic syndromes
- Exam, assess for: HEENT - Horner's syndrome, lymphadenopathy; CV - friction rub, consider pulsus; Lungs - e/o effusion/consolidation; Extremities – Edema, clubbing; MSK - bony pain; Neuro - focal deficits, e/o cord compression
- Labs: CBC, BMP for Na, Ca for hypercalcemia- can consider PTHrP; LFTs for e/o liver mets; paraneoplastic panel on CSF if unexplained AMS, neurologic changes
- Imaging:
  - CT Chest, abdomen, and pelvis (+contrast) to assess for extent of dz, lymphadenopathy, and mets
  - Brain MRI mo gado – for ALL patients except stage 1A
  - PET – helpful in detecting distant mets, supplants need for bone scan
  - SCLC: stop workup at first e/o extensive stage dz, unless candidate for chemo/RT or clinical trial, or for prognostication
- Pathology: Transbronchial or percutaneous core or FNA bx critical to diagnosis.
  - **PEARL**: bx site should be chosen to maximize stage (if lung and liver, go for liver); disfavor bone as decalcifying agents used for bx preparation degrade DNA needed for molecular (genetic) studies
  - Mediastinoscopy – gold standard for staging for LNs >1cm on CT even if not PET avid
  - NSCLC – adenocarcinoma (ADC) vs. squamous cell carcinoma (SCC)
    - ADC vs. SCC – histo features (glandular features/mucin prod vs keratin pearls, intracellular bridging etc); IHC markers only if unclear
    - SCLC – neuroendocrine differentiation ("oat" cell)
  - In advanced ADC, targetable driver mutations such as epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), mesenchymal–epithelial transition (MET), v-raf murine sarcoma viral oncogene homolog B1 (BRAF),

NTRK fusion, RET, KRAS (incidence of all these lower in SCC but still consider testing), as well as PD-L1 expression should be assessed since they guide tx. PDL1 should be checked in SCC (**JNCCN 2021;19:254**)

Staging and Prognosis

NSCLC: Staging based on TNM system and determines prognosis (**J Thorac Oncol 2007;2:706**)

- TX to T4:
  - TX is unknown size though proven on cytology of sputum of fluid,
  - T1-4 involves size of primary and involvement of local structures (bronchus, pleura, chest wall, diaphragm, nerve, pericardium, etc). Malignant pleural effusion = stage IV (M1)
- NX to N3: Unknown, regional, to distal
- MX to M1: Unknown, none, present (1a vs 1b)
- **Prognosis**: Depends on stage (**SEER Stat Fact Sheets, Lung and Bronchus Cancer**)
  - Localized dz: 56% 5-yr survival. Regional dz: 29%. Distant metastatic dz: 5%.

SCLC: Limited or extensive designation

- Limited (60-70%): hemithorax and regional nodes, one radiation port
- Extensive (30-40%): Beyond these areas
- **Prognosis**: Determined by stage, PS, LDH, and gender
  - Limited: Median survival of 15-20 mos. 5y survival of 10-15% (**Cancer 2002;95:1528**)
  - Extensive: Incurable. Survival often < 1y. 5y survival of 2% (**Lancet 2005;366:1385**)

Treatment

NSCLC

- **Stage I and II** – resection (segment/lobe/pneumonectomy + LN dissection) → 33% cure (**Ann Thorac Surg 1995;60:615**)
  - If surgery contraindicated based on comorbidities or patient preference – RT will cure ~20% of patients. Stereotactic body radiotherapy (SBRT) is the preferred modality and allows for ↑ RT delivery to smaller area (**JAMA 2010;303:1070**)
  - Adjuvant chemo in Stage IB & II dz. Cisplatin-based regimens → 5.4% survival benefit at 5 yrs (**JCO 2008;26:3552**)
- **Stage III** – heterogenous group, limited data; tx depends on degree of nodal involvement (**JCO 2015;33:2727**)
  - *Resectable*: Surgery + adujvant cisplatin-based chemo +/- XRT if positive margins
  - *Potentially resectable*: May be able to convert to resectable by induction chemo or chemoRT
  - *Unresectable*: Concurrent platinum-based chemo and XRT followed by durvalumab (anti-PD-L1) per PACIFIC trial demonstrating significantly improved overall survival versus placebo (48 vs 29 mos, **NEJM 2017;377:1919**)
- **Stage IV** – All NSCLC patients receive immune checkpoint inhibitors (ICIs) +/- chemo except those w/ actionable driver mutations (EGFR, ALK, ROS1, etc), who receive targeted kinase inhibitors (TKIs) as first line tx.
  - Chemo principles: use pemetrexed for adenocarcinoma histology, use taxane or etoposide for squamous histology.
- **Immune checkpoint inhibitors** (ICIs) +/- platinum-doublet chemo
  - *Pembrolizumab* (anti-PD1 monoclonal ab): If >50% of tumor cells stain for PD-L1, patients are treated either w/ pembrolizumab monotherapy (based on KEYNOTE-024, **NEJM 2017;375:1823**) or w/ pembro + carboplatin/pemetrexed, (based on KEYNOTE-189, **NEJM 2018;378:2078**). The triplet regimen is usually preferred at MGH. If PD-L1 is < 50%, then carbo/pem/pembro is preferred unless patients may not tolerate chemo.
  - *Atezolizumab* (anti-PDL1): A first-line chemo/IO regimen w/ atezo also FDA-approved based on improved OS compared to chemo alone in IMPower150: Carbo, paclitaxel, atezo and bevacizumab (VEGF inhibitor, **NEJM 2018;378:2288**). Not often used at MGH but one of the only chemo/IO regimens studied in EGFR & ALK+ pts.
  - *Nivolumab* (anti-PD1): This is approved as monotherapy for advanced NSCLC previously treated w/ chemo (above agents are also approved in this setting, **NEJM 2015;373:123**)
  - **PEARL**: ICIs do not work well for NSCLC patients w/ driver mutations
  - AEs: Immune-related adverse events are most worrisome and include pneumonitis, colitis, myocarditis, hypophysitis, etc. ICIs can also exacerbate underlying autoimmune dz (ex. IBD)
- **Targeted kinase inhibitors (TKIs):** Target either mutated kinase currently driving tumor proliferation or else kinase downstream. Class AEs include nausea, vomiting, diarrhea, abnl LFTs, pneumonitis, various ocular toxicities. ALK TKIs a/w cardiac toxicity (sinus brady, QTc prolongation). EGFR TKIs cause dry skin and acneiform rash.
- ALK: TKIs target anaplastic lymphoma kinase (ALK) fusion oncogene
  - *Alectinib*: First line for ALK-rearranged NSCLC following ALEX w/ PFS not reached in alectinib group vs. 10.2mo for crizotinib; approved for 1st line use (**Lancet Oncol 2014;15:1119**)
  - *Ceritinib* – 20x more potent than crizotinib, alternative to alectinib (**NEJM 2014;370:2537**)

  - *Crizotinib* – First TKI approved for ALK rearranged NSCLC, no longer used as first line (**NEJM 2014;371:2167**)
  - *Brigatinib* – Approved for ALK rearranged NSCLC; along w/ alectinib has good CNS penetration for patients w/ brain mets (**JCO 2017;35:2490**)
  - *Lorlatinib* – Approved for ALK rearranged NSCLC; has best CNS penetration of the ALK TKIs (**NEJM 2020;383:2018**)
- EGFR: TKIs target epidermal growth factor receptor (EGFR) tyrosine kinase
  - First-line tx: Five approved drugs: gefitinib, erlotinib, afatinib, dacomitinib and osimertinib. *Osimertinib* is now preferred based on the FLAURA study of osimertinib vs 1st gen drugs (erlotinib or gefitinib) that showed improved PFS 19 mo vs 9 mo (**NEJM 2018;378:113**)
  - Subsequent tx: Resistance to earlier generation inhibitors develops w/in 2y in half of cases due to T790M mutation resulting in hindrance of TKI binding and ATP handling. Osimertinib has activity against T790M but resistance possible via other EGFR mutations or signaling pathways (eg. MET amplification). On resistance to osimertinib, can use chemo (eg. Carbo/pemetrexed) +/- bevacizumab/atezolizumab.
- ROS1 translocation: 1-2% of pts w/ NSCLC, young/never smokers. Treat progressed or chemo-naïve pts w/ crizotinib w/ median PFS 19.2mo (**NEJM 2014;371:1963**)
- BRAF V600E mutation: 1-3% of pts w/ NSCLC, usually smokers. Treated w/ a combination of BRAF inh dabrafenib plus MEK inh trametinib produce median PFS of 9.7mo (**Lancet Oncol 2016;17:984**)
- Oligoprogressive dz: RT or resection of single metastatic lesions (brain, lung etc) that develop while TKI otherwise demonstrates continued activity.

SCLC

- Selected stage 1 SCLC – **surgery**
- Limited stage (LS-SCLC) – combined **chemo/RT** if good PS; chemo consists of platinum agent **(cis or carbo) and etoposide and ICI** (atezo or durvalumab). Radiotherapy provides 5% improvement in 3y survival compared w/ chemo alone (**JCO 2012;30:1692**)
  - **Prophylactic cranial irradiation (PCI):** Controversial. Following chemo, offered to potentially ↑ survival for LS-SCLC in complete remission (**NEJM 1999;341:476**).
- Extensive stage (ES-SCLC)
  - Chemo w/ **platinum** plus **etoposide** plus **ICI** (**Cancer 1979;44:406**, **Lancet 2019;394:1929**, **NEJM 2018;379:2220**)
  - For those w/ residual/stable dz, can consider thoracic RT (**Lancet 2015;385:36**). Role of PCI in ES-SCLC being studied.
  - 2nd line tx: **Lurbinectedin**, **topotecan** or **irinotecan**.

Genitourinary malignancies include cancers of the prostate, bladder, kidney/ureter, testes, and adrenal glands.
GU malignances accounted for ~20% of new CA cases (362K) and 11% of CA-related deaths (68K) in 2020 (**CA Cancer J Clin 2020;70:7**).

Germ Cell Tumors

Epidemiology:

- Most common CA in U.S. men 15-35y w/ 9600 cases w/ ~400 deaths in 2020 (**CA Cancer J Clin 2020;70:7**).
- Generally highly curable. Survivorship care is important, given long-term and potentially morbid adverse effects from tx
- Risk factors: cryptorchidism, spermatic or testicular dysgenesis, 1st deg FHx, prior contralateral testis CA

Cancer Biology:

- Derived from malignant transformation of premeiotic germ cells. Somatic mut. burden is low w/ few "driver mutations" (**Cell Rep 2018;23:3392**). 80% of cases have isochrome of chr 12 w/ two fused short arms. 20% have gain of 12p sequences. Somatic mut. and ↑ copy number can be found in KIT, which plays a role in gonadal dev. (**Lancet Oncol 2004;5:363**, **Hematol Oncol Clin North Am 2011;25:457**).
- **Seminomas** (classical vs. spermatocytic): 50%, AFP always nl (i.e. ↑AFP diagnostic of nonseminoma regardless of tissue path), must be 100% seminoma pathologically to be classified as seminoma
- **Nonseminomas**: 50%, can have ↑AFP; can include regions of seminoma but if any component nonseminoma, is treated as nonseminoma; path report includes all subtypes reported by prevalence.
  - Embryonal carcinoma: pure embryonal carcinoma is relatively rare but can be a component in mixed germ cell tumor. AFP usually normal and if positive, should prompt concomitant consideration of yolk sac tumor
  - Teratoma (mature / immature / malignant transformation): composed of somatic cells from ≥2 germ cell layers and thus can differentiate into cartilage, muscle, mucinous glandular epithelium, and even somatic malignancies (e.g. rhabdomyosarcoma, PNET, others)
  - Choriocarcinoma: Highest propensity to metastasize, generally serum hCG in the thousands
  - Other: Yolk sac or endodermal sinus tumors or Sertoli cell tumor (sex cord-gonadal stromal tumor)

Diagnosis:

- Physical exam: Painless testicular mass, diffuse testicular swelling, hardness, and/or mild-mod pain. If present, pain typically NOT severe (if so, consider other causes e.g. epididymitis)
- Tumor sites: 1° tumor most frequently in testis >> RP/mediastinum/CNS. In fact, most RP tumors are a/w carcinoma of testis even w/o palpable mass. Mediastinal GCTs are usually 1° (**Mod Pathol 2005;18 Suppl 2:S51**).
  - Most commonly metastasizes to RP/para-aortic LNs (AKA the "landing zone") first
  - Other met sites: retrocrural, mediastinal, supraclav LNs > lungs >> liver, CNS, bone (**Mod Pathol 2005;18 Suppl 2:S51**).
  - Inguinal LN involvement is rare, implies disrupted lymphatics from prior surgery or invasion of the epididymis, spermatic cord, or scrotum
  - Seminomas commonly metastasize to lung > other organs. Nonseminomas more likely than seminoma to metastasize to non-pulmonary organs, which portends poorer prognosis
- Initial diagnostic work-up includes a scrotal US & serum tumor markers (AFP, hCG, and LDH)

Staging:

- Metastatic cases classified as good, intermed. and poor risk (see table below) (**J Clin Oncol 1997;15:594**)
- Risk classification depends on 1) seminoma vs. nonseminoma, 2) site of metastasis (non-pulmonary visceral mets = bad), 3) site of primary IF nonseminoma (mediastinal = bad), 4) elevated post-orchiectomy tumor markers
- Obtain CT C/A/P and tumor markers for staging, MRI brain and bone scan only if symptomatic
- Sperm banking before systemic therapy or RT for young patients

Risk classification of Germ Cell Tumors

	Risk	Primary	Mets	Markers	%Cases (%5-yr survival)
Seminoma	Good	Any site	Pulm	Any LDH, any HCG, normal AFP	90 (91)
	Intermed	Any site	Nonpulm	Any LDH, any HCG, normal AFP	10 (79)
Non-seminoma	Good	Testis/RP	Pulm	LDH <1.5x uln, HCG <5K, AFP <1K	30-40 (91)
	Intermed	Testis/RP	Pulm	LDH 1.5 -10x uln HCG 5K-50K, AFP 1K-10K	40 (79)
	Poor	Mediastinal, testis or RP	Nonpulm	LDH >10x uln, HCG >50K, AFP >10K	10 (48)

Treatment:

- General principles:
  - Tumor markers measured should fall rapidly after tx (hCG half life 2d, AFP half life 5-7d) and remain low. Failure to normalize suggests micrometastasis (AKA stage IS)
  - Elevated AFP specific for non-seminoma. hCG elevated in both seminoma/nonseminoma. LDH for staging (**J Clin Oncol 1997;15:594**).
    - DDx: AFP may also be elevated by liver injury, HCC, or other GI malignancies. HCG can be elevated iso exogenous HCG, marijuana use, and heterophile antibody interference w/ assay
  - Surgery is a mainstay w/ radical inguinal orchiectomy
  - In early stage dz, surveillance often preferred over adjuvant tx (chemo or XRT, depending on dx) in young patients to avoid long-term toxicities (CV dz, secondary malignancies)

- Seminoma - exquisitely sensitive to chemo and/or XRT
  - Stage I (no nodal/distant mets AND negative biomarkers)
    - Orchiectomy alone (>85% cure rate) followed by surveillance preferred; adjuvant RT or carboplatin can be considered; median recurrence time of 14mo though late recurrence (>5y) possible (**Urology 2011;78(4 Suppl):S435**).
  - Stage II (nodal but no distant mets)
    - Orchiectomy followed by para-aortic/iliac LN bed XRT (if nodes non-bulky, <3 cm) or chemo (90% cure) (**NEJM 1997;337:242**).
  - Stage III (advanced w/ distant mets / high biomarkers)
    - Primary chemotherapy w/ cisplatin + etoposide (EP) +/- bleomycin (BEP) (**J Clin Oncol 2005;23:9290**); PET useful in seminomas to assess post-chemo masses >3cm (**J Clin Oncol 2004;22:1034**).
- Non-seminoma
  - Stage I (no nodal or distant mets)
    - Orchiectomy + 1 of following: RPLND, adjuvant chemo, or surveillance. 20% will recur w/in 2y after surgery; surveillance requires close guideline-compliant f/u w/ clinic, imaging, markers
  - Stage II (nodal but no distant mets W/ only mildly elevated biomarkers)
    - Orchiectomy + RPLND and/or chemo **(J Clin Oncol 1995:13:2700)**
  - Stage III (advanced w/ distant mets / high biomarkers)
    - Cisplatin-based chemo + post-chemo surgery for residual dz – 70-80% cure
    - All residual masses should be excised because histology is not uniform across sites
    - For those who do not obtain CR or who relapse after CR, cisplatin-based salvage therapy can be pursued (e.g. paclitaxel + ifosfamide + cisplatin (TIP) or vinblastine + ifosfamide + cisplatin (VeIP)
    - High dose chemo w/ autologous stem cell rescue cures some in the salvage setting (**J Clin Oncol 2007;25:247**, **Ann Oncol 2011;22:1054**, **NEJM 2007;357:340**).
  - Transformation: Somatic teratomatous components of non-seminomas may undergo malignant transformation into rhabdomyosarcoma, adenocarcinoma, primitive neuro-ectodermal tumor and others; tx of these is individualized.

Bladder/Ureteral Cancer

Epidemiology:

- 85K new cases of bladder/ureteral CA and ~19K related deaths in US in 2020; male > female (CA Cancer J Clin 2020;70:7).
- Risk factors: HNPCC syndrome (J Clin Oncol 2012;30:4409), tobacco use, occupational exposure to aromatic amines (dye, rubber, aluminum), chronic UTI (ranging from UTIs to Schistosoma), cyclophosphamide, pelvic radiation (Nat Clin Pract Urol 2006;3:327)
- Three broad clinical categories: non-muscle-invasive, muscle-invasive, and metastatic which require different tx approaches

Cancer Biology:

- 90% of CAs in the bladder, ureters, and renal pelvis are urothelial carcinoma, sharing similar epidemiology, biology, and tx approach. Other rarer histologies include squamous cell, adenocarcinoma, micropapillary, sarcomatoid, and small-cell
- Molecular profiling
  - TERT mut. and FGFR3 amplifications, fusions, and mut. can be present in all stages, suggesting role in early tumorigenesis (Cell 2017;171:540)
  - Early stage – Deletions of both arms of chr 9; mut. in FGFR3, PIK3CA, RAS family genes
  - Invasive lesions – Deletions of 8p, 11p, 13 and 14q; mut. in p53, Rb, and CDKN2A

Diagnosis:

- Symptoms: painless hematuria (most common), unexplained urinary frequency and irritative voiding sx
- Initial diagnostic work-up includes cystoscopy + CT urogram (to define upper tract dz), urine cytology
- T staging is based on depth, though preoperative clinical staging only 60% predictive of post-cystectomy path (i.e. substantial risk of under-staging)
  - Ta – papillary
  - Tis – carcinoma in-situ, high grade lesion, precursor of more aggressive variant
  - T1 – invades up to lamina propria/muscularis mucosa but not beyond
  - T2 – invades the muscularis propria (AKA muscle-invasive); T2a – superficial, T2b – deep
  - T3 – Invades perivesical tissue, a – microscopically; b – macroscopically
  - T4 – invades prostate, seminal vesicles, uterus, vagina, pelvic or abdominal wall

Management:

- Non-muscle invasive (70%):
  - Treatment: transurethral resection + intravesical tx followed by surveillance cystoscopy (initially q3m, lessening frequency over time) and urine cytology (latter 13-75% sensitive); 70% will recur or have a new occurrence w/in 5y
  - Addition of intravesicular bacilli Calmette-Guerin (BCG) is given to high-risk non-muscle invasive dz (multifocal/recurrent Ta lesions, carcinoma in-situ, & high grade T1 tumors); reduces recurrence compared to intravesical chemo
  - Cystectomy is indicated following progression in some cases (e.g. recurrent high grade dz despite induction +/- maintenance intravesical BCG)(J Urol 2016;196:1021)(J Clin Oncol 2021;39:2020)
  - Pembrolizumab (systemic, 2y) was recently FDA approved for high risk non-muscle invasive bladder CA unresponsive to BCG (Lancet Oncol 2021;22:919)
- Muscle-invasive disease (30%):
  - Staging includes CT A/P, CXR or CT chest, and bone scan if sx
  - Treatment: Radical cystectomy (standard-of-care) or bladder-sparing trimodality therapy for selected cases
    - Radical cystectomy includes removal of the bladder, prostate, seminal vesicles, proximal urethra, and extended pelvic LN dissection for men w/ addition of TAH/BSO and excision of urethra and portion of anterior vaginal wall for women
    - Urinary diversions are required, three main types (equivalent QOL):
      - Ileal conduit: continually drains to bag attached to anterior abdominal wall
      - Orthotopic neobladder (continence maintained by native urethral sphincter)
      - Continent abdominal diversion: reservoir constructed from detubularized bowel segments (requires straight cath; least favored approach due to complication rate)

        - Bladder-preserving trimodality therapy: maximal transurethral resection followed by concurrent chemoXRT in very select cases (ideal: unifocal tumor, visibly complete TURBT, no tumor-associated hydronephrosis, no CIS, good bladder function)
        - Neoadjuvant cisplatin-based combination chemo (MVAC or GC, see cisplatin-based therapies below) is a Level 1 recommendation w/ meta-analysis showing 14% reduction in risk of death and 5% OS benefit at 5y (**Eur Urol 2005;48:202**)
        - Adjuvant therapy can be considered for patients who did not receive neoadjuvant and had high-risk dz following radical cystectomy; meta analyses suggesting 25% reduction in death, though data used are less robust (d/t small studies, early termination)(**Eur Urol 2005;48:189**)
    - Higher T-stage, lymphatic or vascular invasion all predict higher risk of recurrence ranging from ~35% to 65% at 10y (**J Clin Oncol 2001;19:666**)(**J Clin Oncol 2006;24:3967**)(**J Urol 1988;139:461**)
- Metastatic disease
    - Cisplatin-based therapies currently first-line for metastatic dz in cisplatin candidates
        - Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) and gemcitabine plus cisplatin (GC) have similar efficacy (~15mo medial survival) though GC has improved toxicity profile (less neutropenia, neutropenic fever, sepsis, and mucositis)(**J Urol 1988;139:461**)
        - Cisplatin requires good renal function (GFR >60). Pts are also not candidates if they have grade 2 hearing loss or worse, ≥ NYHA Class III CHF, or ≥ grade 2 neuropathy
        - In immunotherapy candidates, avelumab maintenance therapy following cisplatin-based chemo is standard
        - For cisplatin-ineligible pts, first-line options include checkpoint inhibitors (pembrolizumab, atezolizumab) or gemcitabine/carboplatin followed by avelumab
    - Non-cisplatin chemo: gemcitabine + carboplatin, paclitaxel + gemcitabine, docetaxel + gemcitabine, vinorelbine, pemetrexed
    - Systemic immunotherapy: pembrolizumab, nivolumab, atezolizumab, avelumab
        - Mainteinance therapy avelumab following platinum-based chemo improves OS (**NEJM 2020;383:1218**)
        - For progressive dz, next-line pembrolizumab (preferred by NCCN) or nivolumab, avelumab, or atezoluzmab (**NEJM 2017;376:1015**)
    - Molecularly targeted therapy: Erdafitinib approved for FGFR-altered patients
    - Antibody-drug conjugates: Enfortumab vedotin or sacituzumab govitecan
- Other urothelial tumors: renal pelvis, ureter, and proximal urethra all treated on basis of histology, though simultaneous/metachronous primaries may occur requiring monitoring. Trials are investigating neoadjuvant chemo for upper tract tumors.

Renal Cancer

Epidemiology:

- 73K new cases and 15K deaths in 2020 (**CA Cancer J Clin 2020;70:7**).
- Most commonly presents incidentally on imaging or /w fatigue, weight loss, and anemia; classic triad of hematuria, abdominal pain, and a palpable mass in <10% of cases
- Stauffer syndrome: Signs/sx of hepatic dysfunction as a paraneoplastic effect of localized renal CA that resolves w/ nephrectomy; relatively uncommon
- Risk factors: (note: most cases are sporadic) smoking, obesity, hypertension, acquired cystic kidney dz, von Hippel-Lindau (VHL)(**NEJM 2000;343:1305**)

Cancer Biology:

- Clear cell
    - Most common variant
    - Seen in VHL dz (also a/w retinal angiomas, hemangioblastomas of SC and cerebellum, and pheochromocytomas) d/t loss of VHL tumor suppressor gene on chr 3p – encodes a protein that promotes ubiquitination and destruction of HIF-a. Unregulated HIF-a -> overexpression of VEGF, PDGF-B, TGF-a, EPO -> angiogenesis and tumor growth (**J Clin Oncol 2004;22:4991**)(**Mol Cell Biol 2002;22:7004**)
    - Somatic mutation/deletion/silencing in VHL gene occurs in most sporadic clear-cell carcinomas (**Nat Rev Urol 2019;16:539**)(**Nat Rev Nephrol 2020;16:435**)
- Papillary

- Type II more aggressive than Type I, though typically both are less aggressive than clear cell
- MET RTK mut. in both hereditary and sporadic cases of Type I
- Mutations in fumarate hydratase (HLRCC) and succinate dehydrogenase a/w Type II (**World J Urol 2018;36:1899**)(**J Med Genet 2006;43:18**)

- Chromophobe
  - Typically indolent, uncommonly causing metastasis and CA-related deaths
  - Birt-Hogg-Dube syndrome is a rare, AD disorder w/ hair-follicle hamartomas of face/neck, renal and pulmonary cysts, and multiple renal cell tumors (most often chromophobe-oncocytoma)
- Renal medullary carcinoma
  - Rare malignancy a/w sickle cell trait
  - Aggressive and typically lethal w/in 12 mo. Mean age of presentation is 19y
- Oncocytoma
  - Benign, noncancerous growth, often discovered incidentally
  - A/w tuberous sclerosis and Birt-Hogg-Dube syndrome
  - Can be a/w flank pain, hematuria
- Collecting duct carcinoma ("Bellini duct"):
  - Aggressive course, >50% pts presenting w/ mets and thereafter OS of a few mo.
- Sarcomatoid differentiation can be seen in any subtype and is a/w poor prognosis

Diagnosis:

- Initial work-up includes CT scan w/ contrast (or MRI w/o contrast if low GFR. If dx uncertain, may obtain percutaneous bx (**World J Urol 2010;28:253**)
- Staging
  - Stage I: <7cm, confined
  - Stage II: >7cm, confined
  - Stage III: Extends to major vessels, tissues excluding adrenal gland/Gerota fascia (which encases kidney and adrenal gland); nearby LNs
  - Stage IV: Extends beyond Gerota fascia; any LNs, any mets

Management:

- Local disease:
  - Partial nephrectomy preferred over radical nephrectomy but feasibility depends on size, degree of invasion, anatomy, functional status, and risk for CKD
  - LN dissection controversial, likely low value (**Eur Urol 2009;55:28**)
  - Cryoablation/RFA reasonable in selected cases (e.g. small size tumor, exophytic, uncertain surgical candidate, pt preference over surveillance)(**Cancer 2008;113:2671**)
  - Active surveillance may be considered in select cases of "lower-risk" localized small renal masses w/ slow growth kinetics
- Locally advanced (stage III):
  - Invasion of renal vein or IVC does not preclude surgery but technically difficult
  - Benefit of adjuvant TKI remains unclear. Sunitinib x1yr improved DFS w/o OS benefit in one study and is FDA approved for high risk patients (**NEJM 2016;375:2246**) However, other TKIs have failed to show any difference (**JAMA Oncol 2017;3:1249**)(**NEJM 2016;375:2246**)(**J Clin Oncol 2017;35:3916**)
  - Adjuvant immunotherapy is actively being studied but is not currently standard (**J Clin Oncol 2018;36:TPS4599**)
- Metastatic (stage IV):
  - Several prognostic systems exist to determine risk status and associated median survival taking into consideration these potentially poor prognostic factors: time <1 yr betweendx and need for systemic therapy, poor performance status, elevated Ca, anemia, elevated LDH, elevated ANC, elevated platelets (**J Clin Oncol 1999;17:2530**)(**Lancet Oncol 2013;14:141**)
  - Standard approach is combo immune-oncology agent w/ CTLA-4 inhibitor + PDL-1 inhibitor (e.g. ipiliumuab + nivolumab) OR TKI +PDL-1 inhibitor
  - Recommended regimens for clear cell consist of TKIs +/- immune checkpoint inhibitor (see respective sections below)

	Preferred regimen	Other recommended regimen

Favorable risk	Axitinib/pembroluzmab Cabozantinib/nivolumab Lenvatinib/pembrolizumab Sunitinib Pazopanib	Ipilimumab/nivolumab Axitinib/avelumab Cabozantinib
Poor/intermediate risk	Ipilimumab/nivolumab Axitinib/pembrolizumab Cabozantinib/nivolumab Lenvatinib/pembrolizumab Cabozantinib	Pazopanib Sunitinib Axitinib/avelumab

  - Systemic therapy for non-clear cell is varied based on histology and molecular features (**Nat Rev Urol 2019;16:539**)

- Systemic therapy
  - VEGF-receptor Tyrosine Kinase Inhibitors:
    - Sunitinib: Promiscuous TKI that inhibits VEGF, PDGF, FLT3, c-KIT. Approved for 1st-line or 2nd-line use in IFN-refractory dz. AEs: fever, fatigue, rash, diarrhea, hypertension, hand-foot syndrome, ↑LFTs, myelosuppression including thrombocytopenia, hypothyroidism, and CHF (**NEJM 2007;356:115**)
    - Pazopanib: TKI w/ similar targets as sunitinib w/ efficacy in both tx naïve and IFN-refractory patients. Approved for 1st line or 2nd line use in IFN refractory dz. AEs: similar to sunitinib though w/ less fatigue, hand-foot syndrome, and thrombocytopenia and more serious hepatotoxicity (**J Clin Oncol 2017;35:3916**)
    - Sorafenib tosylate: Broad activity against VEGF as well as c-RAF, BRAF, PDGF, FLT3, c-KIT. Similar efficacy to IFN in 1st line setting and FDA approved for 2nd line use in IFN-refractory patients (**NEJM 2007;356:125**). AEs: similar
    - Cabozanitinib and lenvatinib: Newer oral TKIs w/ activity against VEGFR (as well as others) that have better PFS than everolimus following VEGFR rx progression (**NEJM 2015;373:1814**)(**NEJM 2021;384:1289**)
- Immunotherapy:
  - Ipilimumab/nivolumab has greater response rate and OS compared to sunitinib in the first line setting for intermediate and poor risk patients (**NEJM 2018;378:1277**)
  - TKI + ICI is superior to TKI alone for 1st line therapy (axitinib + pembroluzmab, cabozantinib + nivolumab; axitinib + avelumab)(**NEJM 2019;380:1103**)(**NEJM 2019;380:1116**)(**NEJM 2021;384:829**)
  - IFN/IL-2 therapy: was primary Tx until targeted therapies approved in 2006
    - IFN-α demonstrated RR of 10-20% w/ no additional survival benefit from addition of chemo (**J Clin Oncol 1999;17:2859**)
    - IL-2 demonstrated RR 10-15% in ccRCC w/ durable responses in 4-5% of patients, more effective at higher doses. Remains an option for young patients w/ low risk dz given remains only therapy w/ durable complete responses in some pts
  - mTOR inhibitors:
    - Generally later line agents, w/ studies mostly done prior to availability of immunotherapy
    - Temsirolimus: mTOR-activation causes ↑HIF-1-a and HIF-2-a, so has become a target in RCC, especially after progression on TKI (**NEJM 2007;356:2271**). AEs: rash, asthenia, mucositis, nausea, edema, myelosuppression, metabolic syndrome, pneumonitis
    - Everolimus: Orally active mTOR inhibitor w/ demonstrated efficacy in 2nd line setting following progression on TKI (**Cancer 2010;116:4256**). AEs similar to temsirolimus
- VEGF-targeted therapy in clear cell RCC:
  - Bevacizumab: VEGF neutralizing antibody previously used in conjunction w/ interferon therapy, now being studied w/ immunotherapy (**Lancet 2007;370:2103**)(**Eur Urol 2020;77:e168**). AEs: hypertension, asymptomatic proteinuria

Other Considerations
  - Active surveillance may be reasonable in favorable-risk pts
  - Sunitinib, sorafenib, and temsirolimus have efficacy in metastatic papillary RCC, chromophobe carcinoma, and other types of non-clear cell RCC though data is scarce (**Lancet Oncol 2009;10:757**)(**J Clin Oncol 2008;26:127**)
  - Progression on one targeted therapy may not preclude response to another
  - Cytoreductive nephrectomy to debulk tumor in metastatic setting supported by retrospective data from IFN era; however, recent trials suggest sunitinib alone w/o surgery is non-inferior and surgery may be harmful in intermediate/poor risk pts (**NEJM 2018;379:417**)(**JAMA Oncol 2019;5:164**)

- Bony metastases: affects 33% of RCC patients; monthly zoledronic acid or denosumab reduces risk of skeletal-related events (e.g. pathologic fractures, cord compression)
- Brain metastases: frequent complication of ccRCC; sometimes amenable to resection or radiosurgery which may result in long-term survival (**Clin Genitourin Cancer 2019;17:e273**)

Prostate Cancer

Epidemiology:

- 21% of all newly diagnosed CA in males (~192K), 2nd leading cause of CA-related death in men w/ 10% of all CA-related deaths (33K) in 2020 (**CA Cancer J Clin 2020;70:7**).
- Risk factors: Family history, 5-10% cases are hereditary (HOX13B is high-penetrance gene variant but overall rare contributor)(**NEJM 2012;366:141**), fatty diets; black men have a greater number of precursor lesions and larger tumors compared w/ white men. Protective factors: tomatoes (lycopenes), cruciferous veges, carotenoids, fish, omega-3s (**J Clin Oncol 2005;23:8152**)

Cancer Biology:

- Prostate anatomy:
  - Branching tubuloalveolar glands which secrete prostatic fluid, arranged in lobules and surrounded by stroma. Associated w/ dorsal vein complex and pelvic plexus/cavernous nerves responsible for erection (nerve-sparing technique in radical prostectomy important to maintain erectile function)
  - 70% of CAs arise from the peripheral zone and are palpable by DRE. However, 15% of CAs exist anteriorly in the transition zone and may be better assessed by prostate MRI (**Br J Radiol 2017;90:20160693**)(**NEJM 2018;378:1767**)
- 99% of PCa are adenocarcinomas and rely on androgens to grow. Prostatic intraepithelial neoplasia (PIN) is precursor lesion a/w TMPRSS2-ETS gene fusions that drive androgen-dependent growth (**Science 2005;310:644**)(**Cell 2015;163:1011**); 50% of men w/ PIN will develop CA w/in 5y (**Lancet 2003;361:955**)
- PSA is an extracellular glycoprotein that is regulated by androgens and serves as a biomarker for androgen signaling. $T_{1/2}$ of PSA is 2-3 days and should be undetectable after surgery and ADT. However, PSA also elevated in prostatitis, BPH, bx, and ejaculation.

Diagnosis/Staging:

- Gleason score: Primary & secondary growth patterns are assigned a score from 1-5, where 1 is well-differentiated w/ discrete gland formation and 5 is most undifferentiated w/ complete loss of gland architecture. The score is reported as a sum of 1*+2* = total score (ex: 3+4 = 7). Newer Grade Group system further stratifies Gleason score by prognosis:
  - Grade Group 1: Gleason 6
  - Grade Group 2: Gleason 3+4 = 7
  - Grade Group 3: Gleason 4+3 = 7
  - Grade Group 4: Gleason 8
  - Grade Group 5: Gleason 9-10
- Localized disease
  - T1c: elevated PSA and no palpable dz (most common stage at dx in screened populations)
  - T2a, b, c: affects half a lobe, whole lobe, both lobes, respectively
  - T3a, b: extends through the capsule and invades seminal vesicles, respectively
  - T4: Invades adjacent structures
- Disseminated disease
  - High PSA despite local tx or rising after suggests locoregional dz in lymph nodes and/or distant mets
  - Traditionally, CTAP and 99mTc-MDP bone scan used to evaluate; more recent PCa-specific radiotracer PET scans (PSMA-targeted, fluciclovine) are more sensitive for micrometastases (**Lancet 2020;395:1208**)(**Clin Nucl Med 2017;42:e22**)(**J Urol 2019;201:322**)

Prevention:

- Though PCa is androgen-dependent, studies on 5α-reductase inhibitors showed ↓ low-risk PCa by up to 25% but slightly more high-grade PCa on bx (probably detection artifact). Thus not currently recommended for prevention (**NEJM 2013;369:603**)(**Lancet 2012;379:1103**)

Screening:

- Guideline recommendations: 2018 USPSTF recommended individualized decision-making on PSA screening for U.S. men age 55-69, given risk of over-detection and over-treatment
  - Screening may be beneficial if high-risk (African American, positive FHx)
- Prevalence of prostate CA by screening PSA (**NEJM 2004;350:2239**):
  - <0.5ng/mL - 6.6%
  - 0.6 - 1ng/mL – 10.1%
  - 1.1 - 2.0ng/mL - 17%
  - 2.1 - 3.0ng/mL - 23.9%
  - 3.1 - 4.0ng/mL - 27%
  - Note that no PSA "rules out" PCa (rate of increase matters). W/ a PSA value between 4-10ng/mL, PSA velocity of 0.75ng/mL per yr is suspicious for CA

Management:

- Not all PCa is a clinical threat. At autopsy, 70% of men >80y will have occult (generally low grade) PCa. Disease intervention is based on risk of harm from tumor at that time point
  - Localized dz – local therapy vs. active surveillance, depending on risk of progression
  - Metastatic dz – hormonal therapy / chemo to prevent complications/death
- Localized disease
  - Confined to prostate: management options include surgery, XRT + ADT, or active surveillance w/ choice individualized for each pt based on risk status and pt preference (**NEJM 2016;375:1415**)(**NEJM 2016;375:1425**)(**NEJM 2008;358:1250**)
  - Radical retropubic prostatectomy: goal is to remove prostate while preserving urinary control and potency. Goal: PSA undetectable post-op. 92% w/ complete continence at 1yr and erectile function returning by 4-6mo, though rates vary by surgeon, age, and function prior to surgery
  - ADT w/ surgery
    - Neoadjuvant ADT reduced positive surgical margins but has no effect on overall outcome, not recommended
    - Adjuvant ADT for men w/ localized dz at high risk of relapse similarly not proven efficacious other than for node-positive dz
  - Radiation: either or both of these modalities +/- ADT
    - External beam RT: Conformal tx planning w/ intensity modulation allows delivery of higher doses, improved outcomes. Higher rates of diarrhea and urinary urgency, lower rates of incontinence and impotence
    - Implanted radioactive seeds: Placed w/ CT-guidance allowing for lower radiation to healthy tissue w/ rare incontinence, erectile potency after better than surgery (**NEJM 2008;358:1250**). Limited efficacy w/ extra-capsular extension; favored in low-risk to favorable intermediate risk dz; can be combined w/ EBRT if greater risk for ECE
    - ADT w/ XRT (neoadjuvant/concurrent/adjuvant)
      - Proven mortality benefit of adding ADT to EBRT, unlike in surgery (**NEJM 2009;360:2516**)(**J Clin Oncol 2008;26:585**)(**Int J Radiat Oncol Biol Phys 2005;61:1285**)
      - Neoadjuvant ADT involves typical lead in of 2-8 mo. prior to start of external beam RT
      - Intermediate risk localized: Standard ADT duration is 4-6 mo.
      - High risk localized: Standard ADT duration is 18-36 mo.
      - Benefit of adjuvant versus early salvage XRT for rising PSA remains debated (**Lancet 2020;396:1422**)
  - Cryosurgical ablation and high intensity focused ultrasound (HIFU): Investigational for focal tx of local dz.
  - Watchful waiting/active surveillance: expectant monitoring (w/ interval PSA/imaging/bx) of localized prostate CA, typically in older men and/or men w/ lower-risk tumors. Survival ranged 80-90% for 10-20y w/o intervention (**NEJM 2016;375:1415**)(**NEJM 2014;370:932**)(**Eur Urol 2020;77:713**)
    - PROTECT trial demonstrated equivalent outcomes and low prostate CA-specific mortality at 10y between surgery, XRT, and AS but higher incidence of metastasis w/ AS (**NEJM 2016;375:1415**)

  - If local recurrence: can manage w/ ADT or salvage radiation/surgery if no e/o distant metastasis
  - Biochemical recurrence:
    - Defined as consistently rising PSA w/o mets on scan following local tx
    - May represent local recurrence and/or metastatic dz (typically the latter, micro-mets); options include early ADT vs. delaying until clinical e/o metastasis, w/ possible but unclear benefit w/ early ADT (**Lancet Oncol 2016;17:727**)
- Metastatic castration-sensitive prostate CA
  - Androgen deprivation therapy (ADT): Can be accomplished /w GnRH agonists, GnRH antagonists, or bilateral orchiectomy. GnRH agonist can cause initial testosterone surge and dz flare so should be used w/ extreme caution in pts /w severe pain or spinal cord dz. Lead-in /w AR antagonist used to prevent transient flare by blocking androgen receptor
    - Following initiation of ADT, PSA nadir is prognostic of survival (**J Clin Oncol 2006;24:3984**)
    - Continuous vs intermittent: Controversial. Intermittent ADT seems non-inferior in some studies (**NEJM 2012;367:895**), but was not in another (**NEJM 2013;368:1314**)
    - Agents previously used for castration-resistant prostate CA are increasingly used in frontline setting for hormone-naïve dz due to OS benefit:
    - + chemo: Addition of docetaxel to ADT improves OS compared to ADT alone, though most benefit in high volume dz (**NEJM 2015;373:737**)(**Lancet 2016;387:1163**)
    - + abiraterone/prednisone: addition of abiraterone/prednisone improves OS w/ hazard ratio similiar to addition of docetaxel (**NEJM 2017;377:352**)(**NEJM 2017;377:338**)
    - + AR antagonist: addition of 2nd generation anti-androgen (enzalutamide, apalutamide) to ADT improves OS (**NEJM 2019;381:121**)(**NEJM 2019;381:13**)
      - Loss of BMD: Obtain DEXA at baseline and as clinically indicated thereafter; recommend Ca/Vit D, weight bearing exercise. Bisphosphonate or denosumab in osteoporosis dosing schedule can be considered if risk sufficient to merit pharmacotherapy (**J Natl Cancer Inst 2002;94:1458**)(**J Clin Oncol 2014;32:1143**)(**NEJM 2009;361:745**)
      - Side effects of androgen blockade: erectile dysfunction, loss of libido, mild fatigue, hot flashes, loss of muscle mass, gain of fat mass, mild normocytic anemia, and loss of BMD. Long term use a/w slightly ↑ diagnoses of CAD, DM2, and stroke
- Castration-resistant prostate cancer (CRPC)
  - Defined as dz that progressed while medically castrate (T<50ng/mL) on ADT, can be either metastatic or non-metastatic (rising PSA alone; M0 CRPC)
  - M0 CRPC
    - Addition of apalutamide, enzalutamide, darolutamide to cont. ADT demonstrated OS benefits, leading to recent FDA approval (**NEJM 2018;378:2465**)(**NEJM 2018;378:1408**)(**NEJM 2019;380:1235**)
  - M1 CRPC
    - Multiple agents shown to prolong OS, though limited data on head-to-head comparison or optimal sequence
    - Typical options include androgen-directed therapy (enzalutamide or abiraterone acetate) vs. taxane (cabazitaxel, docetaxel)
    - Other systemic therapies may be considered in select cases (see below) or if already challenged w/ androgen-directed therapy

- Systemic therapy
  - Immunotherapy:
    - Sipuleucel-T: autologous cellular vaccine composed of prostatic acid phosphatase and GM-CSF designed to illicit an immune response to PAP w/ median OS 25.8mo vs 21.7mo (HR 0.78, CI 0.61 - 0.98)(**NEJM 2010;363:411**)
    - Checkpoint inhibitors not shown to be effective in unselected prostate CA patients; however ipilimumab (anti-CTLA-4 ab) w/ nivolumab (anti-PD1) shows activity and remains under investigation (**Cancer Cell 2020;38:489**)
    - Pembroluzimab (anti-PD1) approved for any tumors w/ mismatch repair deficiency (prostate CAs included) and immunotherapy can be considered for tumors w/ CDK12 alterations (**Cell 2018;173:1770**)

- Cytotoxic chemotherapy:
  - Docetaxel: Improved OS compared to mitoxantrone in CRPC. Also effective in high-volume castration-sensitive dz. Significant myelosuppression (may require G-CSF), contraindicated w/ hepatic dysfunction
  - Cabazitaxel: Can use after progression despite docetaxel (**Lancet 2010;376:1147**)
  - Mitoxantrone: first chemo for CRPC. No OS benefit and reserved for palliation in progressed dz; rarely used in current practice
- Androgen-directed therapies:
  - Drugs directed at disrupting the intra-cellular androgen axis targeting intratumoral androgens, activated androgen receptors w/ demonstrated efficacy in CRPC both before and after docetaxel therapy
  - Abiraterone acetate: Oral CYP17 inhibitor that blocks androgen biosynthesis which has OS benefit in multiple contexts and can be considered in conjunction w/ ADT (**NEJM 2017;377:352**)(**NEJM 2017;377:338**) or in tx of CRPC (**Lancet Oncol 2015;16:152**). AEs: mineralocorticoid excess syndrome (fluid retention, HTN, hypoK) esp if not given prednisone
  - Enzalutamide: oral AR antagonist w/ improved OS demonstrated now in non-metastatic (**NEJM 2018;378:2465**) and metastatic CRPC (**NEJM 2014;371:424**) as well as, more recently, castration-sensitive metastatic dz (**NEJM 2019;381:121**). CNS toxicity including seizures occur rarely
  - Apalutamide and darolutamide are newer AR antagonists w/ less toxicity (**NEJM 2018;378:1408**)(**NEJM 2019;380:1235**)
  - Primary resistance to these agents is 20-40% and acquired resistance is near-universal
- Targeted therapy
  - Olaparib, rucaparib, niraparib, and talazoparib are PARP inhibitors effective in tumors w/ homologous recombination repair deficiency by exploiting inefficiencies in DNA repair
  - Olaparib recently showed PFS + OS in mCRPC tumors w/ at least one alteration in BRCA1, BRCA2, or ATM progressed on abi/enza (**NEJM 2020;382:2091**)(**NEJM 2020;383:2345**). Now approved for CRPC harboring a germline or somatic HRD gene mutation (specifically: BRCA1/2, ATM, BARD1, BRIP1, CDK12, CHEK1/2, FANCL, PALB2, RAD51B/C/D, RAD54L), previously treated w/ enza/abi. Toxicities include anemia (12-37%), VTE (7%), and notably, MDS/AML (rare)
  - Ruciparib recently showed PFS improvement resulting in accelerated FDA approval but only for BRCA1/2 mutated CRPC after progression on enza/abi (**J Clin Oncol 2020;38:3763**). Similar toxicities of anemia, GI upset, liver injury, rarely MDS/AML
  - NHiraparib and talazoparib are actively being studied

- Radioactive therapy:
  - Radium 223: Radioactive isotope that is a calcium-mimetic, accumulating preferentially in bone, inducing breaks in DNA. Improves OS for pts w/ metastatic dz to the bone w/o visceral or bulky nodal metastases (**NEJM 2013;369:213**).
  - XRT: focal XRT and systemic xrt can produce palliation, commonly used iso skeletal pain

Malignant Adrenal Tumors

- Rare w/ limited data to guide treatment
- Malignant adrenal cortical carcinoma
  - Derived from adrenal cortex
  - 60% of cases a/w hormone secretion ⟶ s/sx of hypercortisolism, virilization, and mineralocorticoid excess.
  - Prognosis is poor, esp if tumors >5cm or local invasion
  - Treatment
    - Localized dz: managed surgically w/ or w/o adjuvant mitotane
    - Metastatic dz: mitotaine is an adrenocorticolytic agent commonly used w/ low response rates, no OS benefit (**J Clin Oncol 2009;27:4619**); chemo can be used (e.g. etoposide/doxorubicin/cisplatin w/ mitotane)(**NEJM 2012;366:2189**)
- Malignant pheochromocytomas
  - Arise from chromaffin tissue of adrenal medulla, extremely rare accounting for 10% of pheos
  - Sx from secretory lesions include classic triad of HA, diaphoresis and tachycardia
  - Treatment
    - Localized dz: Surgery
    - D/t association w/ VHL, VEGF receptor-targeted agents have been trialed w/o clear benefit.

Overview (CEBP 2017;26:1511, J Natl Cancer Inst 2019;111:60)

- Prognosis remains very poor. 5Y OS <50%, primarily because 70% of new presentations occur as advanced dz.
  - Thought to be d/t fallopian tubes being open to and mobile in the pelvis and ability of female pelvis to accommodate large masses w/o sx.
- Lifetime risk for females 1.3%.

Risk Factors:
- Older age (median age 63Y), PCOS (2.5X), nulliparity (2.5X), endometriosis (2.5X), smoking (2X)
- Genetics: Ashkenazi (10X), BRCA1 (30X = 50% lifetime risk), BRCA2 (13X = 20% lifetime risk), HNPCC (13X), 1st-degree relative w/ ovarian CA (5X)
  - Genetics accounts for ~10% of cases; these often present at an earlier age.

Screening:
- Normal risk: No screening if no symptoms.
- High risk (hereditary, BRCA1, BRCA2, HNPCC):
  - Transvaginal US + CA-125 q6mo starting at age 30-35Y or at 10Y earlier than youngest ovarian CA in family.
  - Patients may prophylactically undergo BSO.

Biological Subtypes:
- Epithelial (95%)
  - Serous (30-70%): resembles fallopian epithelium
    - Low grade: formerly Grade 1
    - High grade: formerly Grade 2-3
  - Mucinous (5-20%): resembles GI epithelium (needs EGD, colonoscopy, CEA to r/o mets from GI CA mets rather than primary ovarian)
  - Rarer: endometroid, transitional, clear cell (resembles renal clear cell, considered high grade)
- Malignant germ cell (5%)
- Malignant sex cord stromal (1%)
- Other: carcinosarcoma (aka malignant mixed Müllerian tumor, aggressive and poor prognosis), borderline epithelial tumors of low malignant potential (grossly appear invasive but microscopically are not invasive)

Symptoms:
- Usually asymptomatic until advanced
- Bloating, abdominal distention, early urinary urge/frequency, early satiety
  - Germ cell: torsion
  - Clear cell: VTE
  - Small cell (very rare): hyperCa
  - Mucinous: large cystic masses filling abdomen/pelvis

Work-up (NCCN 2.2020):
- Exam: abdomen, pelvic
- Transvaginal U/S → CT/MRI CAP w/ contrast (PET-CT OK if indeterminate lesions and would change management)
- CBC/d, CMP, LFTs, baseline CA-125
  - CA-125 is only 20% sensitive in early-stage dz, 80% sensitive in advanced epithelial dz. Only 70% specific (also elevated in breast, bowel, lung CAs; benign ovarian pathology; leiomyoma; hepatobiliary dz). Best used for monitoring rather than dx.
- Early Gyn Onc referral
- Possible diagnostic laparoscopy to evaluate for resectability
- Genetics referral
- Molecular testing of tumor: BRCA1/BRCA2/HRD, MSI/MMR

Staging, Prognosis (NCCN 2.2020):

Stage	Classification	5Y survival
I	A: 1 ovary B: both ovarires C: surface involvement or malignant ascites	IA/IB: 90-95% IC: 85%
II	A: uterus, tubes B: other pelvic organ C: malignant ascites	70-80%
III	A: microscopic abd mets B: macroscopic but ≤2 cm mets C: >2 cm mets, abd LNs	25-50%
IV	liver/spleen mets or mets outside abd	5-19%

Treatment (NCCN 2.2020):

General principles:
- Regardless of stage, resection and debulking ("cytoreduction") is key, though most stages II-IV dz will recur.
- Platinum-based therapies are the foundation, though most tumors eventually become resistant
- Bevacizumab often added to Stage II-IV dz
- Intraperitoneal chemo very toxic, not done often in modern practice

Serous epithelial:
- Surgery (neoadjuvant Carboplatin-Taxol for 3-6 cycles if needed)
- Adjuvant tx: 6 cycles total including any neoadjuvant tx
    - Stage IA/IB, low grade: observe or antiestrogen tx
    - Stage IA/IB, high grade: Carboplatin-Taxol
    - Stage IC: Carboplatin-Taxol
    - Stage II-IV: Carboplatin-Taxol ± bevacizumab
- Maintenance tx:
    - bevacizumab not in primary tx: niraparib (or olaparib)
    - bevacizumab in primary tx: bevacizumab + olaparib (or single-agent niraparib or olaparib)
    - surveillance visits q2-4mo x 2Y, q3-6 mo x3Y, then annually, w/ CA-125 if initially ↑
    - imaging as clinically indicated
- Recurrences:
    - Platinum-sensitive: recurrence ≥6 mo. after primary platinum tx
        - Carboplatin + gemcitabine +/- bevacizumab (JCO 2012;30:2039)
        - Carboplatin + liposomal doxorubicin +/- bevacizumab
        - Carboplatin-Taxol +/- bevacizumab
        - Cisplatin-gemcitabine
        - Carboplatin alone
    - Platinum-resistant: recurrence <6 mo., platinum-refractory: poor response to upfront tx
        - Niraparib, olaparib, or rucaparib alone
        - Paclitaxel +/- bevacizumab (JCO 2014;32:1302)
        - Gemcitabine alone
        - Aromatase inhibitor, Lupron, or tamoxifen

Mucinous epithelial:
- Surgery (neoadjuvant Carboplatin-Taxol if needed), then:
    - Stage IA/IB: observe
    - Stage IC: observe or systemic tx (FOLFOX, CapeOx, or Carboplatin-Taxol for 3 cycles total)
    - Stage II-IV: systemic tx (FOLFOX, CapeOx, or Carboplatin-Taxol for 6 cycles total)
        - ± bevacizumab added to any of FOLFOX, CapeOx, Carboplatin-Taxol

Carcinosarcoma:
- Surgery (neoadjuvant Carboplatin-Taxol if needed), then:
    - Stage I: Carboplatin-Taxol for 3 cycles total
    - Stage II-IV: Carboplatin-Taxol +/- bevacizumab for 6 cycles total

Clear cell:
- Surgery (neoadjuvant Carboplatin-Taxol if needed), then:
    - Stage IA: Carboplatin-Taxol for 3 cycles total or observe
    - Stage IB/IC: Carboplatin-Taxol for 3 cycles total
    - Stage II-IV: Carboplatin-Taxol +/- bevacizumab for 6 cycles total

Endometroid:
- Surgery (neoadjuvant Carboplatin-Taxol if needed), then:
    - Stage 1A-1B Grade 1: observe
    - Stage IC Grade 1: observe or antiestrogen tx
    - Stage II-IV Grade 1: Carboplatin-Taxol for 6 cylcles total then antiestrogen tx or straight to antiestrogen tx
    - Grade 2-3: treat as for serous epithelial

Malignant sex cord stromal tumor:
- Surgery, then
    - Stage I low risk: observe
    - Stage I intermediate-high risk: observe or BEP for 4 cycles
    - Stage II-IV: BEP for 4 cycles
- Recurrent: Carboplatin-Taxol, BEP

Malignant germ cell tumors:
- Surgery, then
    - Stage I immature teratoma or dysgerminoma: surgery
    - Stage II-IV and all other germ cell ovarian CAs: surgery then adjuvant BEP for 4 cycles
- Recurrent: TIP chemo

Borderline epithelial tumor of low malignant potential:
- Complete resection, then observe

Adverse Effects:
- Bevacizumab: bleeding or thromboses, malignant hypertension, GI perf, poor wound healing
- Carboplatin: cytopenias (esp. platelets), electrolyte wasting, hypersensitivity (often starting at lifetime 8-9th dose)
- Taxol: cytopenias, peripheral neuropathy, rarely acute MI
- PARP inhibitors: thrombocytopenia, treatment-related leukemia (~1%)
- Intraperitoneal chemo: severe myelosuppression, infection, nephrotox, N/V/abd pain, neurotox

Overview

Survival: While still deadly, advances in immunotherapy and BRAF targeted therapy have significantly improved survival

Genetic mutations: Sporadic Melanoma (90%): **BRAF (50%), NRAS (15%), KIT (2%). GNAQ** in 50% of uveal melanoma. Hereditary Melanoma (10%): CDKN2A (p14/p16) (25-40%), BRCA2, CDK4, XP genes (**Cancer Biol Ther 2019;20:1366**)

Epidemiology: 1/34 men and 1/53 women will develop invasive melanoma in their lifetime (**CA Cancer J Clin 2015;65:5**); incidence has increased by over 30% in the last 20 yrs

Risk factors: UVB > UVA radiation, blistering burns, intense sunlight/sporadic exposure (men's backs/women's legs), tanning beds. Others include # dysplastic nevi, FHx, light skin/hair/eye color, freckles, immunosuppression

ABCDEs for Recognizing Melanoma:
Asymmetry
Border (irregular, uneven)
Color (black, blue, pink)
Diameter (6 mm)
Evolution (larger, color change, discomfort/itching, bleeding/ulceration)

Prevention and Screening: Reduce sun exposure, wear sunscreen! >SPF 15; regular use can reduce risk by 50% (**JCO 2011;29:257**). Skin exams q6-12m. Supported by data only in those with FHx or ↑# dysplastic nevi

Diagnosis

All suspicious lesions should undergo complete excisional biopsy with 1-3mm margin of nl skin

Subtypes at diagnosis:

- Superficial spreading: (60-70%) median age 50, mixed color, irregular appearance, often arising in precursor mole (BRAF)
- Nodular melanoma: (10-20%) rapidly enlarging, more biologically aggressive/metastatic, elevated or polypoid, blue/black/pink, often not meet ABCDE criteria
- Lentigo maligna melanoma: (10-15%) older patients, arising in situ from lentigo maligna, begins as a tan or brown macule, gradually enlarges
- Acral lentiginous melanoma: (5%) appears on palms, soles, subungual, dark, irreg. borders, flat to nodular (KIT). Most common type of melanoma (35-65%) among dark-skinned individuals
- Mucosal melanomas: (resp, GI, GU mucosa) (KIT)
- Uveal melanoma (iris, choroid, ciliary body): most common metastasis site to liver (80-90%)

Prognostic factors

(1) Tumor thickness, (2) ulceration, (3) mitotic rate

- Mitotic rate indicator of tumor proliferation, measured as number of mitoses per mm2. 2010 AJCC staging system, mitotic ≥ 1 per mm2 a/w worse disease-specific survival (DSS), especially in patients with melanoma ≤ to 1.0 mm thick (**JCO 2009;27:6199**)
- Other poor prognostic signs: Male, >50 at dx, microsatellites, LNs involved at dx, clinically palpable LNs, trunk/head involved at dx
- LDH elevation is a poor prognostic factor
- Patients with V600E or V600K mutations are likely responsive to BRAF or MEK inhibition (see Management below)

Survival

Percentage 10-year melanoma specific survival based on stage at dx **CA Cancer J Clin 2017;67:472**):

- Stage I or II: 75-98% (IA, IB >94%, IIA 88%, IIB 82%, IIC 75%)
- Stage III (LN positive): 24-88% (IIIA 88%, IIIB 77%, IIIC 60%, IIID 24%)
- Stage IV (distant mets): 10-19% historical survival rates relevant for natural history, but 5-year survival rates w/ immunotherapy 26 – 52% (**NEJM 2019;381:1535**, **Lancet Oncol 2019;20:1239**), w/ BRAF targeted therapy 26-34% (**NEJM 2019;381:626**

Staging: AJCC 8th edition:

N Category	Number of tumor-involved regional lymph nodes	Presence of in-transit, satellite and/or microsatellite metastases	T Category								
			T0	T1a	T1b	T2a	T2b	T3a	T3b	T4a	T4b
			No evidence of primary tumor	<0.8 mm without ulceration	<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration	>1.0-2.0 mm without ulceration	>1.0-2.0 mm with ulceration	>2.0-4.0 mm without ulceration	>2.0-4.0 mm with ulceration	>4.0 mm without ulceration	>4.0 mm with ulceration
N0	No regional metastases detected	No	-	IA	IA	IB	IIA	IIA	IIB	IIB	IIC
N1a	1 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N1b	1 clinically detected	No	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N1c	No regional lymph node disease	Yes	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2a	2 or 3 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N2b	2 or 3, at least 1 of which was clinically detected	No	IIIC	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2c	1 clinically occult or clinically detected	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
N3a	≥4 clinically occult (i.e., detected by SLN biopsy)	No	-	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3b	≥4, at least 1 of which was clinically detected, or the presence of any number of matted nodes	No	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3c	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID

T0 — no evidence of primary tumor (e.g., unknown primary or completely regressed melanoma); **Tis** — melanoma in situ;
Tx — thickness cannot be assessed. (Tis and Tx are not included in the table but are part of the staging system.)
Nx — Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason).
Exception: pathological N category is not required for T1 melanomas, use clinical N information. (If an SLNB was performed, the results can and *should* be used for pathological evaluation.)

Management

- Stage I and most IIA: Surgical **excision**, no imaging, +/- Sentinel LN Bx depending on Bx result (usually for higher risk IB and stage II)
- Stage IIB and up: If resectable, wide excision (to fascia, margin depends on 1* depth) +/- sentinel node (SN) Bx (NEJM 2011;364:1738)
  - SN positive: Symptom directed imaging and consider BRAF mutation testing. Consider complete LN dissection (CLND), though it is no longer standard given no difference in OS. Alternatives include nodal basin US surveillance, adjuvant Tx (e.g. immunotherapy or targeted therapy), locoregional RT
  - SN negative: Stage IIA– No further treatment. Follow up with symptom-directed imaging. Stage IIB/C – consider clinical trial, adjuvant tx or observation
- Adjuvant tx options (Stage III, or Stage IV s/p resection of mets): Treatment must be individualized based on mutation status, performance status, pace of disease/sites of involvement, and prior rx. Current practice is 1yr of **PD-1 inhibition** or **dabrafenib/trametinib** (if BRAF mutant)
  - High-dose interferon alfa-2b: historical therapy (JCO 1996;14:7, Lancet 2008;372:117); *AE:* Flu-like sx, fatigue, fever, myalgia, N/V, headache, depression, SI; ↑LFTs, neutropenia, thyroid dysfunction, anemia
  - Immune Checkpoint Inhibition (ICI):
    - **Ipilimumab** (PD1). *AE:* 90% of pts experienced immune-related complication (derm, GI, endo, hepatitis); only 30% of pts continue therapy after

  - **Nivolumab:** superior to ipilimumab with respect to RFS and toxicity (NEJM 2017;377:1824)
  - **Pembrolizumab:** longer RFS compared to placebo (NEJM 2018;378:1789)
  - **Ipi + Nivo:** superior in primary endpoint compared to monotherapy (nivo) (NEJM 2019;381:1535, CheckMate 915 – press release 4/2021– did not meet primary endpoint for PD-L1 negative patients; 64.6 vs 63.2% 2 yr RFS); IMMUNED (Stage IV resected – A) nivolumab plus ipilimumab; B) Nivolumab; C) Placebo – Both ipi/nivo and nivo arms were superior in primary endpoint, RFS, than placebo (Lancet 2020;395:1558)
- Targeted therapy (BRAF mutated):
  - Dabrafenib/Trametinib (NEJM 2017;377:1813), Vemurafenib/cobimetinib, Encorafenib/binimetinib

- Chemotherapy: Single and double agent chemo can produce response, but no improvement in overall survival. **Dacarbazine** is the only FDA-approved chemotherapy for metastatic melanoma, RR 10-20%, long-term CR in 1-2% of pts. AEs: N/V, mild myelosuppression. **Temazolomide** is not FDA approved, but is used in advanced melanoma d/t improved AE profile and similar efficacy. **Paclitaxel** and **Paclitaxel/carboplatin** combination therapy
- Radiation/Surgery: Palliative treatment of symptomatic lesions incl. brain, cord, bone, skin or SQ mets. Oligometastatic disease can be approached with isolated surgical resection often with rapid symptom palliation or occasionally long-term responses
- Surveillance: CT imaging (cross sectional CT chest/abdomen/pelvis +/- brain) q3-12 months for another 2 yrs, then q6-12mo for 3 years to screen for recurrence or metastatic disease

Targeted Therapies

- **BRAF-targeting therapies:** Targetable mutations (% cases): BRAF (50%): BRAF V600E (80%), BRAF V600K (15%), BRAF V600R/M/D/G (5%). Therapies either target mutant kinase or downstream effectors.
  - BRAF inhibitors: **Vemurafenib**: median overall survival benefit 13.6 – 15.9mo (JCO 2013;31:3205), **Dabrafenib**: improved PFS compared to chemotherapy (NEJM 2012;367:107), **Encorafenib** (COLUMBUS, Lancet Oncol 2018;19:603)
  - MEK inhibitors: work immediately downstream of BRAF in the MAPK pathway, **Trametinib** (22% RR alone NEJM 2015;372:30), **cobimetinib**, **binimetinib**
  - Combined BRAF/MEK inhibition: standard of care for BRAF mutants, superior to single agent BRAF inhibitors in RR, PFS, and OS in randomized controlled trials (Lancet Oncol 2016;17:1248, Ann Oncol 2017;28:1631). Downside: ↑ AE compared with mono-tx w/ fever and chills (dabrafenib/trametinib); AKI and ↑ bleeding risk (vemurafenib/cobimetinib). Approved BAF/MEK combinations: **Dabrafenib/trametinib, Vemurafenib/cobimetinib, Encorafenib/binimetinib**
  - General AE: Fever, rash, photosensitivity, SCC, hyperkeratosis, second 1° melanoma, chronic myelomonocytic leukemia expansion, mucosal cancers
  - Outcomes: Often rapid response (i.e. often used in visceral crises); however, CR is uncommon d/t de novo or acquired resistance (AR); AR often occurs within the 1st year of Tx
- **Other gene mutation targeting therapies:** Trials ongoing for PI3K/AKT, angiogenesis, and KIT inhibitors. Variable response of KIT inhibitors (e.g. imatinib, sunitinib, nilotinib) as KIT has multiple mutation hotspots. **Larotrectinib** and **Entrectinib** for NTRK gene fusion-positive tumors. **Binimetinib** for NRAS-mutated tumors

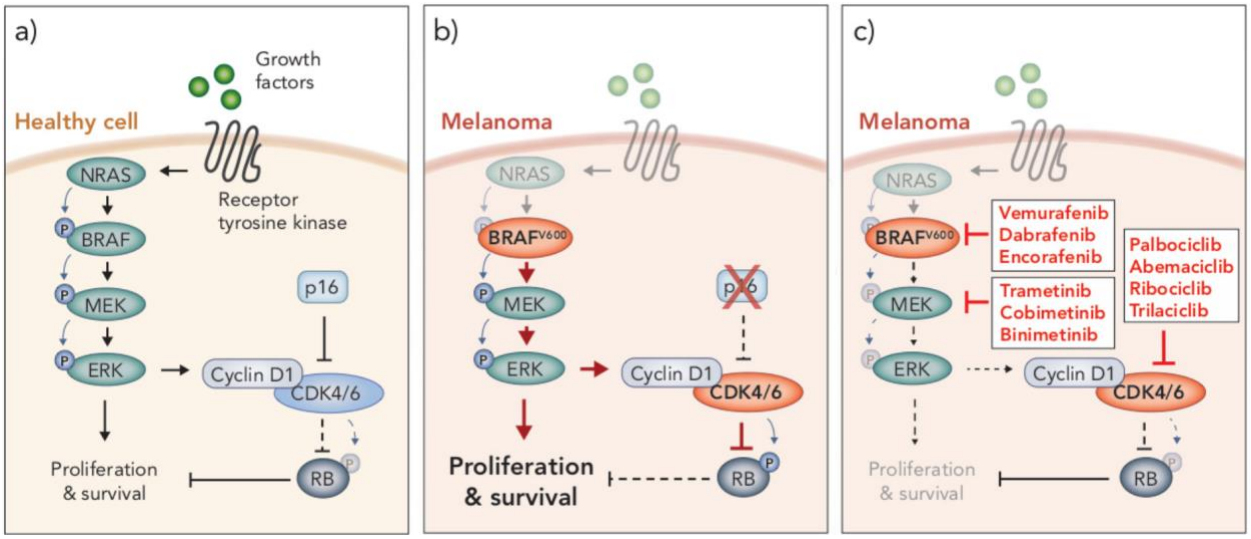


Figure from Lelliot *et al.* 2021 (Front Immunol 2021;12:661737)

Immunotherapies:

PD-1 blocking antibodies: prevent binding of PD-1, a co-inhibitory T-cell receptor, to PD-L1)
• **Pembrolizumab**: Superior to ipilimumab (1yr OS ~70% vs 58%) (NEJM 2015;372:2521), now also approved for Stage IIB/C • **Nivolumab**: 1yr OS nivo 73% vs. chemo 42% (HR 0.42; p<0.001); ORR 40% vs. 13.9% (NEJM 2015;372:320) • AEs: Similar to ipilimumab (above) though less frequent and often less severe
(CTLA)-4 blocking antibodies: directly promotes T-cell antitumor activity and inhibits regulatory T cells
• **Ipilimumab**: Improved OS 10 vs 6mo median OS at one year (NEJM 2010;363:711) and 21 vs 12% at 3y (NEJM 2011;364:2517) when compared to dacarbazine • Response may occur later following a period of "pseudoprogression" and even well after therapy. AEs generally more than PD-1 blockade
PDL-1 blocking antibodies:
• **Atezolizumab:** studied in combination therapies with MAP/MEK inhibitors (IMspire150, Lancet 2020;395:1835). 1y long study, showed to improve PFS by 5 mo if Atezolizumab is added to Vemurafinib/cobimetinib.
LAG-3 blocking antibodies:
• **Relatlimab:** studied in combination with nivolumab, increased PFS by 6 months compared to nivo monotherapy (RELATIVITY-047, NEJM 2022;386:24)
Combination therapies:
• **Ipilimumab + nivolumab** produces higher RR and durable responses in most (NEJM 2015;373:23). Grade 3-4 AEs in 50%, though largely reversible. • **Relatlimab + ipilimumab** (RELATIVITY-047), Grade 3-4 AEs in 18% • **Combination targeted therapies + ICI**: Vemurafenib/cobimetinib + atezolizumab (PDL1 inhibitor) (IMspire150, Lancet 2020;395:1835). Dabrafenib/trametinib + pembrolizumab vs dabrafenib/trametinib (Keynote-022, J Immunother Cancer 2020;8:e001806) - higher PFS, better duration of response, higher toxicity, trend to higher OS
Oncolytic virus:
• **Talimogene Laherparepvec (T-VEC)** injection of attenuated oncolytic HSV-1 → tumor lysis and GM-CSF producing; approved by FDA for intratumoral injection. Patients must have palpable disease and no or limited metastatic disease to be considered. Compared in a randomized trial with SQ GM-CSF, superior durable response rate and borderline improvement in overall survival (JCO 2015;33:2780).
TCR therapeutics:
tebentafusp-tebn (Kimmtrak) chimeric T cell receptor targeting gp100 antigen, fused to CD3 → binds on HLA/gp100 complex of MHCI, directly recruits and activates T cells through CD3. Indication for HLA-A*02:01-positive metastatic uveal melanoma patients (NEJM 2021;385:1196)

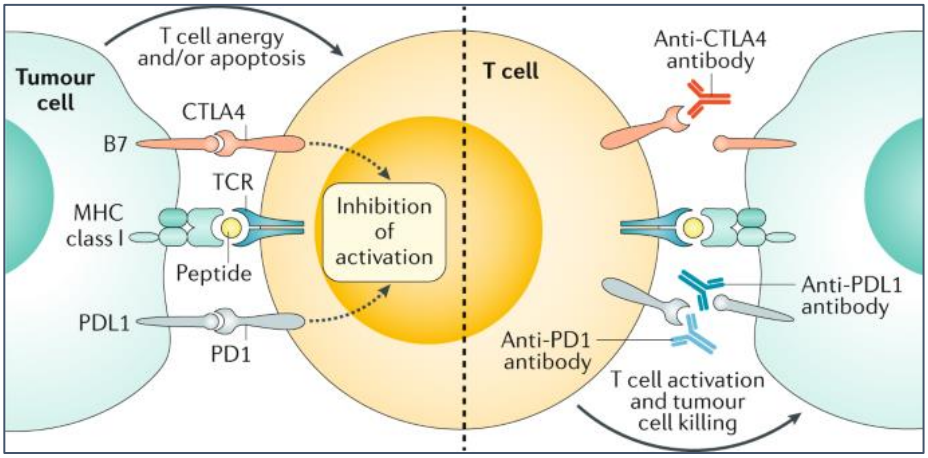
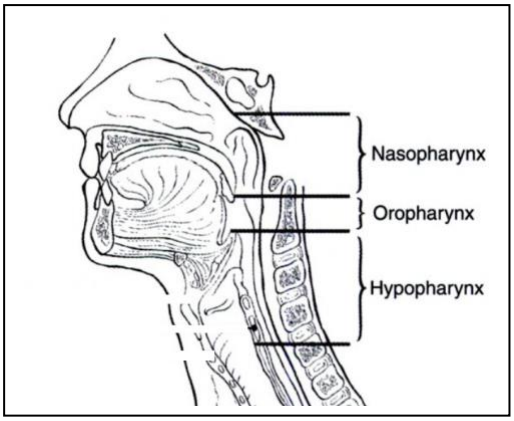


Figure from Ganesh *et al.* 2019 (Nat Rev Gastroenterol Hepatol 2019;16:361)

Overview



- Head and neck CA includes CAs of the following areas:
  - Upper aerodigestive tract: oral cavity (most common), nasopharynx, oropharynx, hypopharynx, larynx
  - Paranasal sinuses
  - Salivary glands
- Oral and oropharyngeal CAs are the 10th most common CAs worldwide and 7th leading cause of worldwide CA-related death.
- Incidence highest in Southeast Asia and lower in developed countries, though HPV-related head and neck CA rising in latter.
- ~50,000 pts diagnosed annually w/ head and neck CA in USA.
- >90% of head and neck CAs are squamous cell (HNSCC).

Risk Factors

- Head and neck CA generally results from external exposures (tobacco, alcohol, viral infections, specific foods).
  - Tobacco and alcohol are culprit in 75% of cases. Risk multiplied when the two combined.
    - Smoking most affects the larynx whereas alcohol most affects the pharynx and oral cavity.
  - HPV-related head and neck CA is increasing in incidence. These CAs have an overall better prognosis, however they often present in otherwise unexpected pts: no smoking or alcohol history, younger than the classic head and neck CA pt (30-50y old compared to >50y old).
- Genetics can play a role, but these are rare causes.

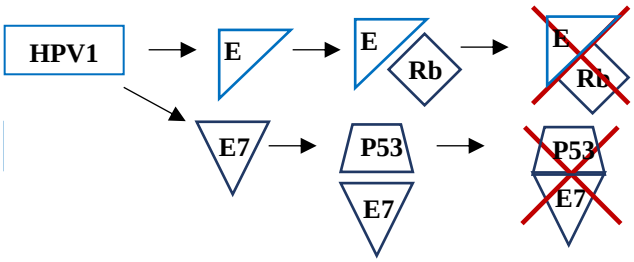
> "Field Cancerization:" risk of second primary cancer in the aerodigestive tract due to smoking or alcohol. This explains the rationale for triple endoscopy for head and neck cancer pts (EGD, bronchoscopy, laryngoscopy).

Pathophysiology

- Molecular alterations:
  - Overexpression: *EGFR, CCND1, PI3K/AKT/mTOR
  - Inactivation: Rb, p53, PTEN
  - HPV-related HNSCC has a different mutational landscape from non-HPV-related dz
    - HPV-related is associated w/ ↓ p53 and CDKN2A, ↑PIK3CA mutations
- Viral effects on molecular profile
  - HPV: proteins E6 & E7 inhibit p53 & Rb, respectively
  - EBV: LMP1 and other proteins ↑ cell replication → nasopharyngeal carcinoma.

> *EGFR is altered in >90% of squamous cell head and neck cancer. Overexpression corresponds to poorer prognosis.

HPV Molecular Alterations



Diagnosis

- Can p/w hoarseness, dysphagia, pain, ulcers, wt loss.
  - If symptoms present >3wks, refer for eval w/ ENT.
- HPI: Ask about smoking, EtOH, sexual hx (HPV risk).
- Physical Exam: Consider triple endoscopy, esp if smoking/tobacco (see "field cancerization" above) or if diffuse e/o dz.
- Imaging: All H&N pts should get a CT or MRI of the neck. The chest should be imaged, too, w/ either a CXR or, in advanced dz w/ CT or PET/CT.

> **Pre-cancer findings:**
> *Leukoplakia: white, hyperparakeratosis + hyperplasia*
> *Erythroplakia: red, epithelial dysplasia*

- Pathology: FNA neck nodes, and if oropharyngeal dz, send specimens for HPV testing:
  - **HPV-associated Squamous Cell Head and Neck CA** (NEJM 2001;344:1125): Most of these are caused by HPV16 (>90%), but HPV18 can cause the same dz. They are typically oropharyngeal and affect younger pts w/o alcohol or smoking histories. There is typically nodal dz at diagnosis, and prognosis is generally better than stage-matched HPV-negative tumors.
  - **Nasopharyngeal Carcinoma**: Different pathophysiology. While uncommon in the USA, nasopharyngeal carcinoma is common in Asia. This CA is associated w/ EBV and salt-preserved foods and is the head and neck CA most likely to metastasize. (EBV can be tested w/ the EBER ISH test.)

HPV Testing:
- P16 immunohistochemistry - most sensitive
- HPV in situ hybridization - most specific
- HPV DNA PCR

Staging
- Staging depends on where the primary CA arose - based on one of five anatomic areas: oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx.
- Staging is based on the TNM system (tumor, nodes, metastasis), the specifics of which vary w/ above anatomic location.

Even stage IV SCCHN is potentially curable (Stage IVA-B dz), if there are no distant metastases (Stage IVC dz).

Treatment (JCO 2015;33:3225)
- Surgery and Radiation are the foundation of therapy for head and neck CA at all stages.
- Early disease managed w/ surgery or RT. Similar cure rates but different short- and long-term adverse effects. Radiotherapy typically results in better organ function (e.g. swallow, speech), though advances in surgery are changing this. RT ↑ risk of mucositis, xerostomia, fibrosis, dysphagia, and necrosis. Definitive RT w/ curative intent requires a multidisciplinary approach including nutrition and SLP to maintain nutritional status (sometimes G tube needed) and swallowing function.
- Locoregionally advanced disease: Multimodality therapy: either combination surgery and RT +/- chemo, or definitive concurrent chemoRT when organ preservation desired, as surgery can be quite morbid (JCO 2013;31:845). Deciding which tx option to pursue is based on tumor location, desire for organ preservation, underlying organ function, baseline performance status of the pt, and institutional expertise. *Chemo is used typically only in advanced dz, but single-agent cisplatin can be given as a sensitizing agent to make RT more effective.
  - Combining cisplatin w/ RT can improve both dz-free and overall survival (JCO 2003;21:92, NEJM 2004;350:1945).
- Recurrent/metastatic disease: In metastatic dz or recurrent dz ineligible for surgery or RT, pts receive platinum doublet tx (carboplatin/paclitaxel most commonly) +/- Cetuximab (EGFR antagonist), which adds 2-3 mo to overall survival (NEJM 2006;354:634, NEJM 2008;359:1116). Immunotherapy also an option for metastatic pts who progress after first-line platinum-based chemo (FDA-approved agents: nivolumab and pembrolizumab).

Follow-Up
- For the first year after tx, pts should return to clinic once every 1-3mo. After 5y, pts can return once a year.
- New imaging should be performed 6mo after tx. If imaging is performed too early, it can show changes concerning for recurrence that are actually post-RT evolution.
- The thyroid often receives some level of RT during tx. This is an organ very susceptible to RT, so be sure to monitor for e/o thyroid CA and hypothyroidism and document risk for pts' primary care providers.
- Signs of recurrence include reappearance of original presenting symptoms (e.g. dysphagia), new pain, ulcers, bleeding or masses, persistent cough, hemoptysis, and hypothyroidism

Sinonasal Tumors:
- These make up 5% of all H&N CAs so are particularly rare.
- Treatment consists of surgery and post-operative RT.
- Prognosis is poor, w/ 5y survival ranging from 30-50%.

Salivary Gland Tumors:
- These make up 6-8% of H&N CAs and are associated w/ RT, smoking, HIV & HBV.
- Salivary gland CAs are typically resected at an early stage, and recurrence is treated w/ re-resection or RT. If recurrent, however, prognosis is typically poor.

Overview (Cancer Cause Control 2014;25:747)

- Cancer of unknown (or occult) primary (CUP) is a malignancy whose primary tumor has not been identified *despite extensive evidence-based work-up*.
- Possible origins:
  - The primary tumor is microscopic or otherwise undetectable.
  - The primary tumor regressed after metastasis.
- Typically, these cancers are widespread, since symptoms are usually 2/2 metastatic burden, and while prognosis may vary, it is typically poor. Median survival is 6-9 months, and the primary tumor is ultimately found in fewer than 30% of patients.
- CUP represents 2-5% of all newly diagnosed cancers, or over 30,000 per year. General subgroups of CUP are: Adenocarcinoma, squamous cell carcinoma, neuroendorcrine neoplasm and poorly differentiated cancer from unknown primary site.

Diagnosis (NCCN 2.2021)

H&P
- Personal hx cancer, biopsies, excised lesions, spontaneously regression lesions
- Last age-appropriate cancer screening, prior imaging
- Family hx cancer
- Tbco, EtOH, IVDU hx

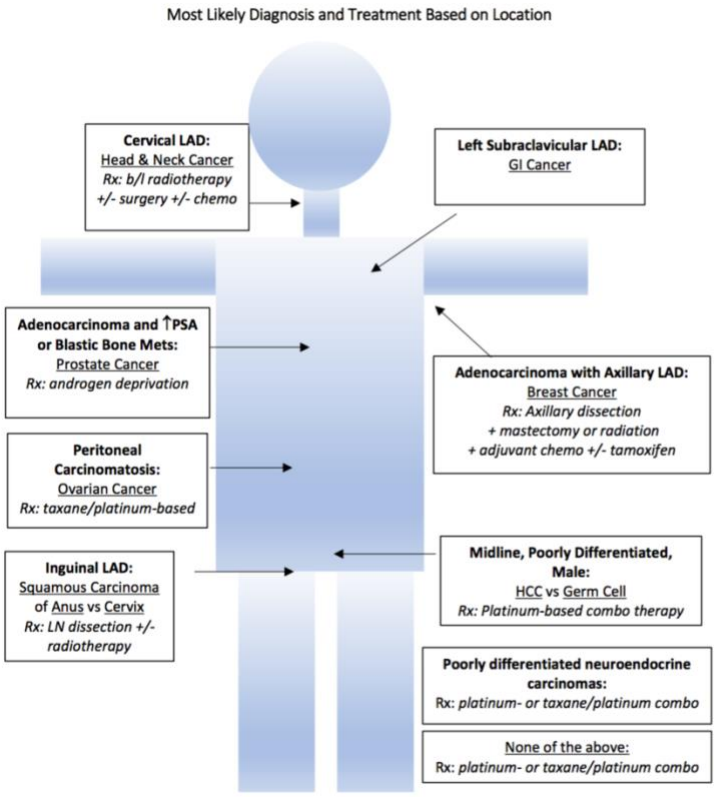
Physical Exam
- includes skin, LNs, thyroid, breast, pelvic, testicular, rectal

Labs
- CBC/diff, LFTs, BMP
- UA, FOBT
- Consider PSA in men >40Y
- If clinically indicated: CEA (pancreatic, colon, breast), CA 19-9 (pancreatic, colon), CA 15-3 (breast), CA-125 (ovarian, breast), β-hCG (germ cell), AFP (HCC)

Imaging/studies
- CT (or MRI) CAP w/ contrast (PET-CT is *not* standard of care)
- If clinically indicated: mammography, testicular US, EGD, colonoscopy
- Liver malignancy: 18-40X more likely to be a met than a primary HCC, cholangiocarcinoma, or gallbladder carcinoma
- Bone mets: common in breast, lung, prostate, RCC
  - osteolytic: MM, RCC, thyroid, melanoma, lymphoma, uterine, GI, HCC, sarcoma, SCC
  - osteoblastic: prostate, osteosarcoma, chondrosarcoma
  - mixed: breast, lung, cervical, testicular

Pathology
- Core biopsy (>> FNA). Consult Oncology for biopsy site
- Bone biopsy difficult because decalcification damages DNA and limits molecular testing
- If at this point no primary identified: dx is Cancer of Unknown Primary
- Ask Pathology for TMB, MSI/MMR testing Snapshot/Fusion testing to direct tissue-agnostic therapy
- **Classification system:**
  - Mod. diff. adenocarcinoma (60%)
  - poorly diff. adenocarcinoma (25%)
  - SCC (5%)
  - undiff. carcinoma (5%)
  - neuroendocrine (5%)
  - poorly differentiated NOS (5%)
  - lymphoma, thyroid carcinoma, melanoma, sarcoma, germ cell

General Principles
- There currently is no indication for genome sequencing. This is an evolving topic of debate and can be discussed on a case-by-case basis.
- The liver is a common site of metastasis for most solid tumors. A liver tumor is 18-40x more likely to be a metastasis than a primary tumor. The liver tumor work-up involves first determining primary vs met. (Primary liver tumors: HCC, cholangiocarcinoma, gallbladder carcinoma)
- Bone metastases → commonly arise from breast, lung, prostate, or renal cell carcinoma.
- Osteolytic lesions: MM, Renal Cell Carcinoma, Thyroid, Melanoma, Lymphoma, Uterine, GI, HCC, Sarcoma, SCC
- Osteoblastic: Prostate, Osteosarcoma, Chondrosarcoma o Mixed: Breast, Lung, Cervical, Testicular o **All above can present differently, but these are typical patterns.*
- "Cannot Miss" Diagnoses:
  - bone mets → watch for pathologic fracture, spinal cord compression, severe hypercalcemia
  - If suspect lymphoma → tumor lysis syndrome (monitor K, Phos, Ca, Cr)



Suspected cancer	Tumor Marker
Pancreatic	CEA, CA19-9
Colon	CEA, CA 19-9
HCC	AFP
Ovarian	CA-125
Breast	CA 15-3
Germ Cell	bHCG

Secondary studies adenocarcinoma:

Finding	Added labs	Added imaging/studies
cervical LAD	PSA	skull base + neck CT (or MRI) w/ contrast
supraclavicular LAD axillary LAD	PSA	neck CT (or MRI) w/ contrast, mammogram
mediastinal involvement	β-hCG, AFP, PSA	mammogram, testicular US if ↑ β-hCG/AFP
pulmonary nodules, pleural effusion	CA-125, PSA	mammogram
peritoneal involvement, ascites	CA-125, PSA, urine cytology	mammogram, consider cystoscopy
RP mass	CA-125, PSA, β-hCG, AFP, urine cytology	mammogram, testicular US, consider cystoscopy
inguinal LAD	CA-125, PSA	consider proctoscopy
liver involvement	AFP	mammogram, EGD, colonoscopy
bone involvement	PSA	bone scan or PET, mammogram
diffuse mets	PSA	mammogram

Secondary studies squamous cell carcinoma:

Finding	Added imaging/studies
head LAD, cervical LAD, supraclavicular LAD	skull base and neck CT (or MRI) w/ contrast
inguinal LAD	anal endoscopy, consider cystoscopy
bone involvement	bone scan or PET, mammogram

Treatment (NCCN 2.2021)

- If disease is localized, then resect and irradiate
- Treat as such: melanoma, lymphoma, thyroid carcinioma, sarcoma, germ cell, neuroendocrine
- Treat as if primary:
  - Cervical, supraclavicular adenocarcinoma/carcinoma/SCC → head and neck cancer
  - Mediastinal adenocarcinoma/carcinoma → poor-risk germ cell if <50Y or NSCLC if ≥50Y
  - Peritoneal/ascites and ovarian histology → ovarian
  - RP mass and germ cell histology → poor-risk germ cell
  - Mediastinal SCC → NSCLC
  - Axillary LNs/pleural effusion and breast marker positive → breast cancer
- Tx for everything else:

Adenocarcinoma → platinum-taxane if possible	
[carboplatin | cisplatin] + [paclitaxel | docetaxel]	NSCLC, gastric, esophageal
gemcitabine + [cisplatin | docetaxel]	NSCLC, bladder
CapeOx | FOLFOX | FOLFIRI	GI primary
irinotecan + [carboplatin | gemcitabine]	SCLC
capecitabine | fluorouracil w/ leucovorin	GI primary if treating w/ single agent only

SCC	
[carboplatin | cisplatin] + [paclitaxel | docetaxel]	head and neck, esophageal, NSCLC
FOLFOX	gastric, esophageal
gemcitabine + cisplatin	head and neck
cisplatin + fluorouracil	historically used for head and neck, esophageal, anal
capecitabine | fluorouracil w/ leucovorin	skin primary if treating w/ single agent only
cisplatin + docetaxel + fluorouracil	young and fit, possibly more effective but more toxic

- Tumor-agnostic Tx (Nat Rev Drug Discov 2020;19:383):
  - MMR deficient, MSI high, or TMB high → pembrolizumab (ORR 40%, CR 7%)
  - NTRK fusion → larotrectinib, entrectinib (OR 57-76%, CR 7-22%)
  - Many in "basket" trials (RET inhibitors, KIT inhibitors, HER2 targeting)

Prognosis (Tumour Biol 2011;32:45)

Favorable (treat to cure, minority of cases)	Poor (treat to palliate)
• Able to have a likely diagnosis/primary • Midline, poorly diff. • Female w/ papillary adenocarcinoma in peritoneum • Non-papillary malignant ascites • Female w/ adenocarcinoma and one axillary LN involved • SCC involving cervical nodes • Isolated inguinal LAD • Poorly diff. NET • Male w/ blastic bone mets and ↑ PSA • Single, small, resectable	• Adenocarcinoma w/ liver mets • Bone mets • Lung/pleural mets • Brain mets

Overview

- Brain metastases are the most common intracranial tumors in adults (J Neurooncol 2005;75:5).
- With systemic malignancies, brain mets occur in 10-30% of adults and 6-10% of children (CA Cancer J Clin 2021;71:7)
- Generally, median CA survival once brain mets are found, ranges from 3-11mo (untreated, median survival of pts w/ brain mets from solid tumors is 1-2mo). Key predictors of survival after dx of brain mets have been shown to be Karnofsky performance score, extent of extracranial dz, and age.

Risk Factors

- The majority of brain mets arise from carcinomas, including lung CA, melanoma, renal cell CA and breast CA.
- Of note, the brain tends to be the first site of relapse in HER2+ breast CA and EGFR positive non-small cell lung CA.

Between 30-40% of new brain metastasis presentations occur w/ a single metastatic tumor.

Symptoms

- Pts may present w/ a myriad of neurologic symptoms, dependent on the location of the met. These include headache (40-50%), cognitive dysfunction (30-35%), seizure (10-20%), and stroke.
- Significant intracranial hemorrhage occurs in 20-50% of pts (varying degree based on primary CA, e.g. risk is 4x higher in melanoma and renal cell carcinoma, as compared to lung CA)

Diagnosis

- MRI w/ gadolinium more sensitive, but CT head often the first imaging modality.
- When to image varies depending on the CA. In CAs that classically metastasize to the brain (e.g. melanoma, small cell lung CA, HER2+ and triple negative breast CA), brain imaging is part of the initial diagnostic work-up. For other CAs, imaging is not indicated unless pts are experiencing symptoms.

Brain Metastases Locations	
Cerebrum	80%
Cerebellum	15%
Brainstem	5%

DVT Prophylaxis & Treatment

- Heparin and heparin products are generally safe to use in the setting of brain mets, even in pts w/ hemorrhagic mets or tumors at risk for hemorrhage (melanoma, renal cell carcinoma, thyroid CA, choriocarcinoma). However, decisions to initiate AC need to be weighed w/ the risks. Data regarding the risk of AC in pts w/ hemorrhagic brain mets is limited and recent data suggests that it is safe (Blood 2015;126:494). However, pts should be monitored for new neurologic symptoms. If there is concern in the setting of starting AC for pts w/ hemorrhagic brain mets, reasonable to obtain head CT after initiation to reassess.
- IVC filters are not recommended, given the risk of these becoming niduses for clots. If having to decide on how to manage an identified DVT, heparin and enoxaparin are typically safer options than IVC filters.

Heparin and enoxaparin do not increase the risk of intracranial hemorrhage, even in the setting of hemorrhagic metastases.

Blood Brain Barrier

- The BBB classically prevents medication administration through a variety of mechanisms. Tight cell junctions create physical barriers, but there are also prominent drug efflux receptors, the most prominent of which is P glycoprotein. The BBB is violated in the setting of metastatic dz, which increases the likelihood of drug delivery to brain mets, but some medications classically penetrate more effectively (see below) and others that do not (e.g. Traztuzumab). Research also shows RT increases permeability of the BBB.

Treatment (NCCN Guidelines v2.2021)

- For symptomatic control: **Corticosteroids** may improve neurologic symptoms in up to 75% of pts w/ cerebral edema. Pts are not started on steroids in the absence of symptoms, since the side effects may impact quality of life.
  - Dexamethasone is preferred and can be given IV or PO.
  - If symptomatic in house, give 4 mg dexamethasone Q6H.
  - Ideally taper after 2 weeks to avoid steroid side effects.

- For symptomatic control: **Anti-Epileptic Drugs (AED),** ~20% of pts w/ new brain mets p/w seizures for which pts are prescribed AEDs. If pts undergo surgical resection, short-term AED ppx lowers post-op seizure risk by 40-50%. In general, for pts w/ brain mets. AEDs should be prescribed if a pt has seizures or in the postoperative setting.
  - Preferable agents: levetiracetam and lacosamide. Gabapentin can also be considered, but levetiracetam and lacosamide have much better anti-seizure activity.
  - Avoid phenytoin and carbamazepine because these may interfere w/ chemo.

Preferred AEDs in Brain Metastasis:
Levetiracetam
Lacosamide

- Surgery: Surgery can aid in diagnosis, palliation, or local control.
  Palliation: Indicated if tumor ≥3 cm in the posterior fossa (to prevent herniation +/- hydrocephalus), and in the setting of hemorrhagic or large cystic tumors.
  Local control: Indicated for solitary tumor (particularly w/ the right molecular profile) or if there is a large symptomatic mass in the setting of multiple brain mets

- Whole brain radiation (WBRT): Typically for pts w/ multiple mets. Achieves better dz control when in conjuction w/ surgery (**Lancet 2004;363:1665**). Whole brain RT can also be used to treat pts at high risk of developing mets w/ small cell lung CA. However, WBRT can also cause significant neurocognitive decline and reduced QoL (**Lancet Oncol 2009;10:1037**).

- Stereotactic Radiosurgery (SRS): SRS alone can be used in the initial management of pts w/ a limited number of brain mets (usually 1-4) that are appropriate targets for SRS (ie, <3 cm in diameter), as it can have less morbidity than surgery or WBRT. A note of cauton: preliminary studies suggest an increased incidence of symptomatic RT necrosis (feared complication of SRS) in pts receiving SRS for brain mets and concurrent immunotherapy (**JAMA Oncol 2018;4:1123**)

- Chemotherapy, targeted therapy and immunotherapy:
  When choosing systemic tx for pts w/ brain mets, it is important to consider agents that penetrate the blood brain barrier (see table below). If a pt has more than 4 mets, there is no single plan, given there is no randomized data to direct guidelines. Additionally, immunotherapy has shown clinically meaningful intracranial efficacy in recent trials though further research is needed in the field (**NEJM 2018;379:722**).

Medications that Penetrate the Blood Brain Barrier
Cisplatin
Etoposide
Capecitabine
IV Methotrexate
Bevacizumab
Temozolomide
(combined w/ other agents)
Osimertinib (EGFR inhibitor)
Alectinib (ALK inhibitor)
Nivolumab/Pembrolizumab*

*if already attached to a circulating effector immune cell

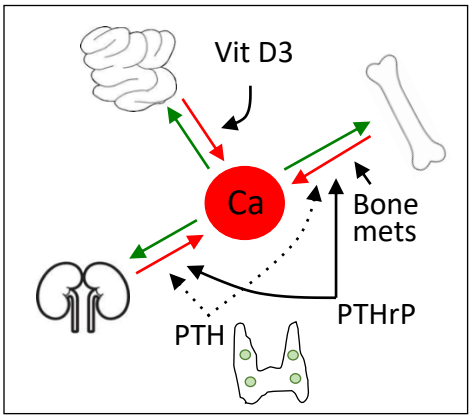
- If you have pts w/ brain metastases interested in clinical trials, please contact Dr. Priscilla Brastianos, Director of the Brain Metastasis Clinic, at **PBrastianos@MGH.harvard.edu**.

- If you would like input on the management of pts w/ brain metastases, there is a weekly multidisciplinary brain metastasis tumor board (Wednesdays at 4:30, Yawkey 9E conference room). Please send email to Dr. Brastianos w/ pt details or feel free to stop by.

Hypercalcemia of Malignancy

Pathophysiology:

- Humoral Hypercalcemia of Malignancy
  - Most often production of PTH related Protein (PTHrP)
  - PTHrP stimulates osteoclasts to proliferate (via RANKL) to break down bone and for the kidney to increase calcium reabsorption
  - Most common cause (80%)
  - Common culprits: SCC of lung, head, and neck, RCC, bladder, breast, ovarian.
- Osteolysis
  - Bone destruction and dissolution from extensive bone metastases
  - Bone metastasis produce cytokines including osteoclast activating factors and/or PTHrP locally, leading to local stimulation of osteoclasts to breakdown bone
  - Common culprits: breast, MM, lymphoma
- Excess production of Vitamin D analogues by malignant cells
  - Extrarenal, PTH independent production of calcitirol (1,25-$(OH)_2$-Vit D) from 25-$(OH)_2$-Vit D which stimulates Ca absorption, and to a lesser extent, osteoclast breakdown of bone
  - Common culprits: Hodgkin, NHL, granulomatous disease (e.g. Sarcoidosis)



Ca homeostasis: Intestinal secretion, renal filtration and bone formation decrease serum Ca (Green arrows). Intestinal absorption, bone resorption, renal reabsorption increases serum Ca (red arrows). Black arrows represent positive regulation in malignancy.

Presentation:

- Symptoms: lethargy, confusion, anorexia, nausea, constipation, polyuria, polydipsia
- Signs: Bradycardia, QT shortening, prolonged PR, cardiac arrest
- Exam may show volume depletion, impaired cognition, signs of cancer

Diagnosis:

- iCa (preferred), corrected Ca = Ca + (0.8 x [4.0 – Albumin])
- Etiology: PTH, PTHrP, Vit D 1,25-$(OH)_2$-Vit D, 25-$(OH)_2$-Vit D
- If no known malignancy: SPEP, UPEP, serum free light chains initially

DDx:

- Non-parathyroid mediated (vitamin D intoxication (25-OH > 150), hypercalcemia of malignancy, chronic granulomatous disorders), parathyroid mediated (familial hypocalciuric hypercalcemia, primary hyperparathyroidism, inherited variants, tertiary hyperparathyroidism (renal failure)), medications (thiazides, lithium, Vit A, theophylline, teriparatide), hyperthyroid, adrenal insufficiency, acromegaly, milk-alkali syndrome, pheochromytoma, parenteral nutrition

Treatment:

- Mild hypercalcemia (<12 mg/dL)
  - Immediate treatment not required, rather advise to avoid factors that aggravate hypercalcemia including thiazides, lithium, volume depletion, prolonged inactivity, and high calcium diet (>1000 mg/day). Encourage 6-8 glasses of water/day to minimize risk of nephrolithiasis. Can consider IV bisphosphonates.
- Moderate hypercalcemia (12-14 mg/dL)
  - Includes as above. In addition, if acute rise in calcium may have lethargy, stupor, and other changes in sensorium. Treat with saline hydration and bisphosphonates as described below.
- Severe hypercalcemia (>14 mg/dL)
  - Volume expansion with isotonic saline initial rate 200-300 ml/hr then adjusted to maintain urine output of 100-150 ml/hr. Loop diuretics only recommended if volume overload from renal failure or heart failure.
  - Calcitonin 4 U/kg (onset with 4-6 hr) repeated q6-12 hrs. Tachyphylaxis to calcitonin may develop after 24-48 hours so should be discontinued before then.
  - Concurrent administration of zoledronic acid (4 mg IV over 15 minutes) (onset of action 24-48 hr) or (less favorably given inferiority in reversing hypercalcemia related to malignancy) pamidronate (60-90 mg over 2

hours). Bishphosphonates will be effective by 2nd -4th day maintaining control of hypercalcemia. Of note, they have a risk of jaw osteonecrosis and need to be dosed for renal insufficiency.
    - If bisphosphonates are contraindicated due to severe renal impairment, denosumab (RANKL inhibitor onset of action in 3 days) may be administered concurrently with calcitonin.
- With calcium in 18-20 range and neurologic symptoms, may consider the above in addition to dialysis.
- Preventing recurrence through disease management. In addition, consider discontinuing or modifying drugs that contribute to hypercalcemia and renal failure, including, but not limited to calcium, vitamins A and D, lithium, thiazide diuretics, antacids, levothyroxine, tamoxifen, NSAIDs.
- May also consider glucocorticoids for patients with chronic granulomatous diseases and some with lymphoma through inhibiting conversion of 25-OH -> $1,25\text{-}(OH)_2$

Tumor Lysis Syndrome

Pathophysiology: metabolic derangements 2/2 en mass lysis of neoplastic cells.
- Nucleic acids → uric acid → precipitation in renal tubules → AKI → hypovolemia → ATN
- Inorganic phosphates → calcium phosphate precipitation → hypocalcemia and nephrocalcinosis
- Potassium release → hyperkalemia

Risk stratification and prophylaxis: In clinical practice, not a strict classification

	Low risk (<1%)	Intermediate risk (1-5%)	High risk (>5%)
Solid Tumors	Myeloma Other solid tumors	Neuroblastoma Germ-cell tumors Small-cell lung cancer	
Chronic Leukemia	CML CLL	CLL and WBC >50k	CLL treated with venetoclax
AML	WBC <25k	WBC <25k but LDH >2X ULN WBC >25K but <100K	WBC >100k
ALL		WBC <100k and LDH <2x ULN	WBC <100K but LDH >2x ULN WBC >100K
Lymphoma	Hodgkin Follicular Mantle cell T-cell lymphoma	Burkitts stage I-II	Burkitt's stage I-II and LDH >2x ULN Stage III-IV Burkitt's Bulky DLBCL
TLS Therapy	Hydration + Allopurinol 300mg PO qD	Hydration + Allopurinol 300mg PO qD	Hydration + Allopurinol 300mg PO BID Consider rasburicase

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CML: chronic myeloid leukemia; CLL: chronic lymphocytic leukemia

- Low risk: Monitor TLS labs daily, IVFs $3L/m^2$ daily, consider allopurinol.
- Intermediate risk: Monitor TLS labs q8-12h, IVFs $3L/m^2$ daily, allopurinol
- High risk: Monitor TLS Labs q6h, IVFs $3L/m^2$, Rasburicase (3mg) if uric acid elevated >8, then if normal can consider using allopurinol.

Diagnosis:
- TLS labs: BMP, iCa, Mg, Phos, Uric Acid, CBC w/diff, LDH, EKG. Supporting lab: elevated LDH.

Cairo-Bishop Criteria

Laboratory TLS Criteria			Clinical TLS Criteria
Defined as >2 of the below present within 3 days before or 7 days after initiating chemotherapy:			Laboratory TLS plus ≥1 of the following: - Creatinine ≥1.5 times ULN - Cardiac arrhythmia or sudden death - Seizure
Uric acid	≥8.0 mg/dL	or 25% increase from baseline	
Potassium	≥ 6.0 mEq/L	or 25% increase from baseline	
Phosphorus	≥ 4.5 mg/dL	or 25% increase from baseline	
Calcium	≤7.0 mg/dL	or 25% decrease from baseline	

Treatment:

- Avoid medications that can exacerbate electrolyte derangements
  - Thiazide, K-sparing diuretics (HCTZ, spironolactone)
  - ACE inhibitors/ARBs

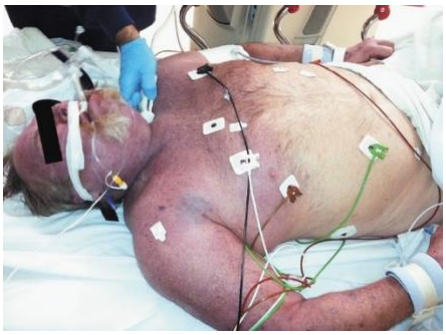
- Hydration
  - Rate: 2-3 L/m^2/day
  - Mechanism: promotes excretion of uric acid and phosphate
  - Goals: TBB even, UOP 80-100 mL/m2/h, urine spec grav ≤1.010
  - Avoid alkalinization
    - Theory: Uric acid is more soluble at basic pH. However, there is no difference between normal saline and alkalinization; instead, you decrease calcium-phosphate solubility

- Supportive care for electrolyte abnormalities
  - Hyperphosphatemia:
    - Moderate (≥6.5) → aluminum hydroxide, calcium carbonate, sevelamer, lanthanus carbonate
    - Severe → dialysis
  - Hypocalcemia (≤7)
    - Asymptomatic → no therapy (do not replete calcium unless symptomatic, risk of calcium-phosphate precipitate)
    - Symptomatic → calcium gluconate
  - Hyperkalemia:
    - K 6.0 - 7.0 and asymptomatic → kayexylate
    - K >7.0 or symptomatic → calcium gluconate, sodium bicarbonate, IV insulin + D50W, Dialysis
  - Uremia → dialysis or hemofiltration
  - Consider HD for severe phosphate elevations (Ca-Phos product ≥70mg^2/dL^2), severe hyperkalemia, severe oligouria or anuria and volume overload.

- Urate-lowering therapy

Agent	Mechanism	Dose	Onset	Pearls
Allopurinol	Xanthine oxidase inhibitor; blocks conversion to uric acid	300 mg PO daily or BID	24+ hrs	• Initiate at least 12-24 hrs prior to chemotherapy • Duration: 7+days or until >72 hrs after completion of chemotherapy • Dose reduce 50% in renal failure • Cost of IV > rasburicase and less effective • Side effects: rash, GI upset, increase liver enzymes
Rasburicase	Recombinant urate oxidase; converts uric acid to allantoin (urine soluble)	3-6mg x1 dose	hrs	• Contraindicated with G6PD deficiency • Side effects: methemoglobinemia or hemolytic anemia (G6PD deficiency) • Caution in pts unwilling to accept blood products (Jehovah's witness) • Re-check uric acid ≥4 hours after dose • Causes degradation of uric acid in blood samples; place samples on ice

SVC Syndrome (Mayo Clin Proc 2017;92:609)



(NEJM 2014;371:1142)

Pathophysiology:

- Compression or occlusion of the SVC, often secondary to thoracic malignancies.
- Masses in the middle/anterior mediastinum, R paratracheal or precarinal nodal regions.
- Often more severe if the occlusion is inferior to azygos vein since the azygos is critical to collateralization to offload returning blood.

Presentation and Diagnosis:

- Common: dyspnea, orthopnea, cough, sensation of fullness in the head and face, headache worse with stooping.
- Less common: chest pain, hemoptysis, hoarseness, dizziness, syncope.
- Exam: face/neck/arm swelling, dilated subcutaneous veins of the chest, neck and proximal arm (Figure 2). Especially worrisome symptoms include stridor (laryngeal edema) and AMS → needs emergent therapy.
- Work up: CT chest and neck w/ IV contrast (MRI if poor renal fxn)

Treatment:

- Elevate the head of the bed, supplemental O2.
- Consult vascular interventional radiology for endovascular stenting.
- In non-emergent cases, radiation therapy is effective.
- Consider steroids

Hyperviscosity (Mayo Clin Proc 2017;92:609)

Pathophysiology:

- 2/2 high levels of monoclonal proteins in Waldenstom's Macroglobulinemia (WM) and MM.
- Hyper-viscosity leads to Impaired capillary blood flow resulting in ischemia.
- IgM more likely than IgG/IgA to cause hyper-viscosity as it exists as a pentamer
- Non-linear relationship between levels of a monoclonal protein and symptoms.
- Symptoms are generally unlikely with viscosity <4cP which correlates to IgM <3g/dL.

Presentation and Diagnosis:

- Symptoms: headache, dizziness/vertigo, seizures, concentration difficulties, impaired consciousness, tinnitus, changes in vision, bleeding, dyspnea, heart failure, priapism.
- Labs: increased serum viscosity (usually >4cP), elevated Immunoglobulin levels (IgM > 3g/dL), Rouleaux formations on smear.
- If concerned, page hematology fellow and clinical pathology resident (p61828) for emergency viscosity study.

Treatment:

- Can temporize with phlebotomy and normal saline replacement.
- Plasmapheresis (attending level decision).
- Treatment of the underlying monoclonal gammopathy.

Leukostasis (Mayo Clin Proc 2017;92:609)

Pathophysiology:

- Leukemic blasts occlude the microvasculature due to their numbers, size, altered deformability, and abnormal expression of adhesion molecules. There is no clear correlation between symptoms and WBC counts (possibly due to adhesion molecules).
- Common culprits: AML > ALL. Can rarely be seen with CLL, CML, and severe erythrocytosis and thrombocytosis.

Presentation and Diagnosis:

- Presentation: fever (>69%), Respiratory distress (23-39%; often with infiltrates on CXR), neurological symptoms (15-30%; blurry vision and other visual deficits, confusion, delirium, headache, dizziness, gait instability), DIC (20-40%), renal failure (16% of AML) (**Leuk Lymphoma 2000;39:1**)
- Typically with WBC counts >100k; but >50k with AML.
- Lab artifacts: spurious hyperkalemia (use ABG), spurious paO_2 (use Pulse Ox), PLT count over-estimated on auto-diff.

Treatment:

- Cytoreduction (all attending-level decisions):
  - Induction chemotherapy: serves to rapidly decrease WBC count (e.g., 7+3 for AML)
  - Hydroxyurea (50-100 mg/kg per day): typically reserved for patients with asymptomatic hyperleukocytosis and awaiting (or unable) to receive immediate induction chemotherapy
  - Leukapheresis: typically reserved for symptomatic patients who must have induction chemo postponed (mortality benefit has not been shown)(**Leuk Res 2014;38:460**). Page Blood Bank.
  - Steroids: consider for ALL prior to induction chemo
- Give IVF/PLT to avoid hemorrhage. Avoid pRBC transfusions.
- Patients are at high risk for TLS and DIC
  - Monitor labs.
  - Initiate prophylactic TLS treatment as above.

Spinal Cord Compression

Pathophysiology:

- Prostate, lung, and breast account for ~1/2-2/3 of cases; others include myeloma, lymphoma, sarcoma, kidney, bladder, unknown primary.
- Usually caused by vertebral body metastases eroding into the spinal canal.
- Mechanism: direct compression or ischemia 2/2 vascular occlusion.

Presentation and diagnosis:

- Symptoms: back pain prior to onset of any neurologic symptoms, weakness and gait instability, ataxia, sensory deficits, autonomic dysfunction (late), cauda equina syndrome.
- Signs: weakness, increased reflexes, + Babinski, reduced anal tone
- Thoracic (60-70%) > lumbosacral (20-30%) > Cervical (10%).
- Work up: MRI of entire spine (cervical, thoracic, and lumbar) with cord compression/metastasis protocol (w/ and w/o contrast) within 24 hours. 2nd line: CT with or without myelography.

Treatment:

- Low threshold for Dexamethasone 10 mg IV followed by 4mg q6h (give prior to imaging if high suspicion).
- Definitive therapy: surgery, radiation, surgery → radiation, or chemotherapy. Not all tumors are radiosensitive, some are radioresistant tumors which is why likely consult neurosurgery (to evaluate for surgical decompression) and radiation oncology.

Brain metastases

Pathophysiology:

- 150,000-200,000 people diagnosed each year, compared to ~17,000 primary brain tumors yearly. 30% of patients with solid tumors develop brain metastatic disease. 80% occur in cerebral hemisphere, 15% in cerebellum, and <5% in brainstem.
- Frequently in watershed areas of arterial circulation and at junction of grey and white matter.
- Lung, breast, and skin (melanoma) cancer account for 67-80% of patients with brain metastases.
- Frequently cause cerebral edema and increased intracranial pressure due to vasogenic edema 2/2 leaky capillaries, stasis from venous drainage, and obstruction of CSF by the tumor.

Presentation and diagnosis:

- Most patients have known cancer; however, can sometimes be first presentation of malignancy.
- Symptoms: headaches (most common), motor/sensory deficits, speech disturbance, unsteadiness, cognitive decline, seizures (10-20% of patients), stroke (5-10%) secondary to hemorrhage into a brain met.
- Diagnosis: MRI brain with contrast, CT head with contrast when MRI contraindicated, and NCHCT if hemorrhage suspected. Biopsy should be performed when diagnosis of brain met is in doubt, especially in patients with a single lesion.

Treatment:

- Prognosis has improved with median survival > six months for all major cancer types. Prognosis is now being individualized by cancer type and molecular genetic diagnosis. A diagnosis-specific graded prognostic assessment (GPA) is used for each major cancer type to determine prognosis.
- Cerebral edema and intracranial hypertension:
  - Always consider whether signs of impending herniation that would be a medical emergency which may require additional interventions than below.
  - Dexamethasone IV (or PO) 4-8mg/d divided once or twice daily. For mod/severe symptoms, consider 10mg loading dose IV followed by initial maintenance dose of 16mg daily in 2-4 divided doses orally followed by a taper.
- Seizures:
  - Lorazepam 4mg IV @ 2mg/min, can repeat x1 PRN in 5 minutes if seizure continues.
  - Pts who experience a seizure due to a brain tumor should be treated with AED given high risk of recurrence.
- Definitive treatments:
  - Resection, radiation, or chemotherapy depending on patient's GOC, underlying cancer, practicality of approach. Obtain neurosurgery consult and radiation oncology consult.

See Section 8.9 of this Manual for more information on Brain Metastases

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Brain Metasteses

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Venous Thromboembolism (VTE) in Cancer Patients

Epidemiology:
- 4-7x ↑ risk of VTE and 3-4x higher rate of VTE recurrence relative to patients without CA.
- Anticoagulated CA patients also have a 2-3x ↑ rate of major bleeding.
- VTE is the second leading cause of death in CA patients, only behind the CA itself.
- CA patients with VTE have more hospitalizations, a higher rate of metastatic dz, and worse overall survival compared to CA patients without VTE across multiple tumor types

Tumor site of origin	First VTE rate per 100 person-years (95% CI)	Percent of total cancer-associated VTE
Pancreas	14.6 (12.9-16.5)	3.9
Brain	12.1 (10.3-14.0)	2.5
Ovary	11.9 (10.6-13.2)	9.5
Stomach	10.8 (9.5-12.3	3.6
Lung	10.1 (9.5-10.8)	13.9
Uterus	7.0 (5.9-8.3)	4.2
Colon	6.7 (6.3-7.2	12.5
Blood	4.5 (4.1-4.8)	10.1
Prostate	4.4 (4.0-4.7)	17.5
Breast	3.2 (2.9-3.4)	15.1
Bladder	2.7 (2.4-3.0)	4.8

Bottom line:
The thrombophilic stimulus of malignancy may be exceedingly difficult to control with competing complications of VTE recurrence and bleeding.

Biology of CA-Associated VTE:
- ↑ tissue factor expression by tumors
- Release of tissue-factor bearing microparticles
- Elevation of soluble P-selectin
- Elevated plasma levels of plasminogen activator inhibitor type 1(PAI-1) resulting in reduced physiologic fibrinolysis
- Elevated markers of platelet hyperreactivity
- Platelet-leukocyte interactions such as platelet-indued neutrophil extracellular trap (NET) release

Risk Factors:
- High Risk Malignancies: Pancreas, brain, lung, and ovarian (see above table). However, most CA related VTE iso of breast, prostate, lung and colon Ca given higher prevalence
- CA stage is critical in assessment of risk; metastatic dz equates 20x ↑ risk of first VTE
- Cytotoxic chemo results in endothelial injury
- Other therapies like biologic agents targeting VEGF (e.g., bevacizumab), TKI's (e.g., ponatinib), immunomodulatory agents (e.g., thalidomide, lnalidomine), hormonal therapies (e.g., tamoxifen, raloxifene), and suppostive therapies (e.g., erythroipoesis-stimulating agents, megestrol acetate, glucocorticoids)
- Patient characteristics: poor performance status, older age, smoking, obesity, sedentary lifestyle/immobility

Inpatient prophylaxis:
- Most hospitalized CA patients with active illness or reduced mobility should be given thromboprophylaxis in the absence of bleeding or other contraindications
- Routine pharmacologic thromboprophylaxis doesn't necessarily need to be offered to patients admitted for the sole purpose of minor procedures or chemo infusion, nor to patients undergoing stem-cell/bone marrow transplantation.

Agent	Standard Dosing	Renal Dosing	Obesity Dosing (BMI >40)
Enoxaparin	40mg SC daily	30 mg if CrCl < 30 ml/min	Consider 40mg SC Q12H
Unfractionated heparin	5000 U SC Q8-12H	No change	Consider 7500 U SC Q8H
Fondaparinux	2.5mg SC daily	Caution if CrCl 30-49 ml/min, avoid if < 30 ml/min	Consider 5mg SC daily

Outpatient primary thromboprophylaxis:
- Although CA is a/w a high risk of VTE, routine pharmacologic thromboprophylaxis should not be offered to all outpatients with CA.
- High-risk outpatients with CA (e.g, Khorana score 2 or higher) may be offered thromboprophylaxis with apixaban, rivaroxaban, or LMWH if no significant risk factors for bleeding and no drug interactions.
- Patients with multiple myeloma receiving thalidomide- or lenalidomide-based regimens should be offered aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients (SAVED, IMPEDE scores)
- Thromboprophylaxis also recommended up to 4 wks post-op for high risk abdominal/pelvic surgeries

Patient Characteristic	Points
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal)	1
Prechemotherapy platelet count ≥ 350,000/μL	1
Hemoglobin level < 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11,000/μL	1
Body mass index ≥ 35 kg/m^2	1
Calculate total score, adding points for each criterion in the model	
Interpretation	
High-risk score ≥ 3 points	
Intermediate-risk score = 1-2 points	
Low-risk score = 0 points	

Trials for Primary Thromboprophylaxis:
- AVERT: 574 patients randomized to apixaban 2.5 mg BID vs placebo. VTE: 4.2% vs 10.2% (HR 0.41; 95% CI, 0.26 to 0.65). In modified ITT analysis, major bleeding in 3.5% vs 1.8%.
- CASSINI: 841 patients randomized to rivaroxaban 10 mg QD vs placebo. VTE: 2.6% vs 6.4% (HR 0.40; 95% CI, 0.20 to 0.80). Major bleeding 2.0% vs 1.0%.
- Both trials required Khorana score of 2 or higher.
- Study population heterogeneity and high drop-out rates make clinical interpretation difficult.

Considerations for Management of Cancer-Associated VTE:
- Superficial venous thrombosis: at least 6 wks AC for non-peripheral catheter-related SVT in proximity to deep venous system. Conservative management and observation with repeat US can be considered if (1) upper extremity (unless close to axillary vein) OR (2) distal lower extremity and <5 cm.
- DVT/PE: at least 3 mo. AC; indefinite if CA active or under tx. Reassess q3mo.: inconvenience, adherence, CA status, GOC, bleeding and other AEs.
- Catheter-associated DVT: No need to remove catheter but consider if no longer necessary. Treat for duration that catheter is in place, then 3 mo. afterwards.
- Splanchnic Vein Thrombosis: At least 6 mo. AC, consider advanced therapies like pharmacomechanical thrombectomy, TIPS, etc. Includes hepatic (Budd Chiari), portal, mesenteric, venous veins; can be acute or chronic and cause portal HTN, intestinal ischemia. ↑ risk with abd mass or surg, cirrhosis, pancreatitis, MPNs with JAK2 mutation.
- DVT in patients with brain mets: Generally safe, but patients with primary brain tumors and melanoma are at high risk for bleeding.

Anticoagulants for Cancer-Associated VTE:
- LMWH: Previously established as standard of care for tx of CA-associated VTE based on results of several trials (most notably CLOT) comparing LMWH (dalteparin) against vitamin K antagonist therapy.
- DOACs: Recent trials (Hokusai-VTE: edoxaban; Select-D: rivaroxaban; ADAM-VTE and CARAVAGGIO: apixaban) have demonstrated DOACs as non-inferior to LMWH in VTE recurrence. However, ↑ signal for bleeding (especially upper GI and possibly GU) seen with DOACs, particularly in patients with gastric and gastroesophageal tumors. This signal has not been seen in the apixaban trials.
- Although DOACs are often the preferred agent, the data for these agents are still being assimilated by many oncologists. If care outside of MGH system or unable to arrange hematology referral, consider starting LMWH therapy and asking outpatient oncologist about preferred AC agent before jumping to DOAC therapy.

Agent (VTE treatment)	Standard Dosing	Notes
DOAC -Preferred for patients WITHOUT gastroesophogeal and genitourinary lesions	Apixiban - 10mg BID x1wk -> 5mg BID Endoxoban - 5 days LMWH or UFH first - 30 or 60mg QD Rivaroxaban - 15mg BID x3wks -> 20mg QD Dabigatran - Above DOACs preferred - 5 days LMWH or UFH first - 150mg BID	- All are Xa inhibitors except dabigatran (DTI) - Idarucizumab is dabigatran reversal agent - Andexanet alfa is newly FDA approved pan-Xa inhibitor reversal agent - Use caution in severe renal insufficiency - Avoid in significant liver dz (ALT/AST > 2x ULN, bili>1.5x ULN) - Consider drug-drug interactions with inhibitors/inducers of CYP3A4 and P-glycoprotein - Limited published data for use when platelets < 50K. Prefer LMWH.
LMWH (Enoxaparin) - Preferred over Warfarin based on CLOT trial -Preferred for patients with gastric or gastroesophogeal lesions	1 mg/kg BID (Alternative 1.5 mg/kg QD though need to be aware of high peak and low trough)	- Can monitor anti-Xa - Consider half dose for mild thrombocytopenia (25-50k) - Reversible w/protamine - Renally cleared
Unfractionated heparin	IV: 80U/kg load -> 18U/kg/hr SC: 333U/kg load -> 250U/kg Q12H	-Target PTT 60-80 -Reversible w/protamine (1mg/100U UFH, max 50mg) - Half-life 4 hours
Fondaparinux	<50kg: 5mg SC daily 50-100kg: 7.5mg SC daily >100kg: 10 mg SC daily	- Can monitor anti-Xa - Long half-life - Renally cleared
Warfarin	2.5-5mg QD, adjust to INR 2-3	- Need to bridge from parenteral agent initially - Reversible with FFP/PCC, vitamin K - Preferred in advanced renal dysfuncton and extremes of weight (< 50 kg or > 150 kg

Contraindications to Anticoagulation:
- Absolute: CNS bleed or hemorrhagic mets; major bleeding requiring >2 units RBC transfusion in 24 hours
- Relative: plt<50K, severe plt dysfunction (ex. uremia), antiplatelet therapy; hemorrhagic coagulopathy, high risk for falls, recent major surgery, CNS mets

Other considerations:
- Anticoagulation failure (Extension of DVT or new DVT/PE while on therapeutic AC): consider HIT, increase dosing and/or frequency, or switch agents (LMWH preferred)
- Trousseau's Syndrome: migratory thrombophlebitis in CA patient – also with warfarin resistance, thrombocytopenia, DIC, thrombotic endocarditis, arterial emboli (treat with UFH, LMWH, or fonda)
- Indications for thrombolysis: life-threatening proximal DVT/PE, intestinal splanchnic vein thrombosis with high risk for ischemia, symptomatic iliofemoral DVT (can limit post-thrombotic syndrome)
- When to consider retrievable IVC filter: contraindication, nonadherence, or failure of AC; severely compromised cardiopulmonary function; CTEPH (2B)

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Etiology:

Benign causes: more commonly small bowel
- Postsurgical adhesions
- Radiation enteritis
- Infectious/inflammatory (abscess, phlegmon)
- Constipation (fecal impaction), ileus (pseudo-obstruction)
- Mass effect from ascites

Mallignant causes: more commonly large bowel, from ovarian, colorectal, gastric CAs (**Oxford Textbook of Pall Med, 5th ed. 2015; sec 14.3, 919**) or less commonly mets from breast, lung, melanoma.
- Intraluminal lesion (colorectal CA) – most common
- Extrinsic compression: peritoneal, omental, or mesenteric tumor involvement

Presentation/Diagnosis:
- Sx: N/V, colicky/crampy abdominal pain, bloating, absence of flatus/BM
  - Proximal (stomach, prox small bowel): acute symptom onset, nausea temporarily resolved after vomiting, metabolic alkalosis/hypoK
  - Distal (colon, rectum, distal small bowel): progressive symptom onset, more abdominal distension with hypoactive bowel sounds (absent peristalsis)
  - Obstipation: inability to defecate or pass flatus indicates a complete obstruction whereas paradoxical diarrhea or fecal incontinence (overflow diarrhea) suggest partial obstruction
- Potential complications: intestinal ischemia, perforation, peritonitis
- Dx: KUB (upright and lateral) can detect high-grade SBO (air fluid levels, bowel distension) but gold standard is CT A/P with PO contrast (can diagnose strangulation, differentiate etiology of bowel obstruction, characterize grade of obstruction by flow of contrast), occasionally MRI abdomen (better detects peritoneal and hepatic dz)

Management of Malignant Bowel Obstruction:
- Consider interventions based on multidisciplinary decision (**Support Care Cancer 2001;9(4):223**), (**Ann Oncol 2016;27(suppl 5):v119**), involve palliative care team early)
- Decompression with NG tube or endoscopic G tube ("venting PEG"); self-expanding colonic stent (sometimes as bridge to surgery)
- Surgical (including resection, lysis of adhesions, ileostomy/colostomy, bypass): consider in pts with peritonitis/pneumoperitoneum, signs of ischemia on imaging, fever/leukocytosis/tachycardia. Contraindications include ascites, peritoneal carcinomatosis, advanced age, poor performance/nutritional status, or not within patient's goals of care.
- Medical:
  - Antiemetics: IV Haldol (first choice), olanzapine, scopolamine/glycopyrrolate, dexamethasone (avoid prokinetics if complete obstruction)
  - Antisecretory drugs: octreotide/lanreotide (can be given as depot), anticholinergics
  - IV fluids for hydration
  - Pain control with opioids
  - No evidence for parenteral nutritional support
- Treat underling CA with systemic chemotherapy once clinically improved- often course of action in GI malignancies where malignant obstruction is a common presentation

Overview

Incidence: 20% of patients who receive systemic anti-neoplastic therapy or a stem cell transplant may develop some sort of pulmonary toxicity

Symptoms: Dyspnea, cough, new hypoxemia or hypercarbia, insidious weight loss, fatigue
Timing: Days to mo. after receiving chemo; can be after the first dose or after cumulative doses

Mechanism: heterogeneous, including but not limited to:

- Post-infectious changes
- Direct injury to pneumocytes or alveolar capillaries ⟶ inflammatory response
- Systemic cytokine release ⟶ capillary leak and pulmonary edema
- Lymphocyte and macrophage activation ⟶ cell-mediated injury, free radicals, impaired repair
- Radiation induced injury or sensitization to future injury

Initial Workup and Framework for a Differential Diagnosis:
Remember to distinguish between intrinsic pulmonary manifestations a/w oncologic disease and true pulmonary toxicities from oncologic tx!

- Initial: Review history (malignancy, chemo, XRT, surgery, other comorbidities) and start w/ CXR (PA and Lateral if doable), basic labs (including a blood gas), and consider an EKG.
- CXR: is there an obvious problem in the pleura, airways, mediastinum, lung tissue?
  - If pleural effusion, consider non-con chest CT (better for effusion size), or proceed straight to diagnostic +/- therapeutic thoracentesis (vs. chest tube/PleurX)
  - If lung tissue, consider causes as per below ⟶ may need CT to better view parenchyma.
  - Note: any malignancy increases risk for PE. However, do not just default to CT-PE as non-contrast CT may provide higher image quality for lung-parenchymal process
- Chest CT: Is the problem in the alveoli? Interstitium? Airways? Vasculature/heart? Pleura?
  - Consults: Pulmonology & Infectious Disease (especially to r/o infection, DAH, pneumonitis); consider bronchoscopy w/ BAL +/- transbronchial biopsy
- Systemic glucocorticoids: Often warranted in severe pulmonary toxicity, but r/o infectious etiologies first (some pathologies are not steroid-responsive ex: UIP, vaso-occlusive disease)

1) Rule out non-specific processes that can be commonly found in cancer patients:

a) **Cardiogenic pulmonary edema**
W/u: EKG, troponin, NT-proBNP, CXR, TTE
- Review for known cardiac disease, XRT to chest (direct cardiac damage vs coronary artery sclerosis), cardiotoxic chemo hx: anthracyclines, cyclophosphamide

Tx: Diuresis, cardiac management

b) **Pulmonary embolism**
W/u: EKG, troponin, NT-proBNP, CT-PE, V/Q scan if needed, LENIs
Tx: Anticoagulate if no contraindication

c) **Infection**
W/u: Pan-culture incl sputum (bacterial, fungal, AFB, consider PJP), Flu/RSV, Beta-d-glucan, Galactomannan; consider serum Crypto, urine Histo, Blasto, Cocci
- If CXR does not show a clearly focal process, non-con chest CT
- Consider ID consult +/- Pulm consult for bronch w/ lavage +/- biopsies

Tx: antimicrobials

d) **Bland alveolar hemorrhage**
2/2 edema/infection/inflammation/coughing iso thrombocytopenia/coagulopathy
W/u and Tx: Transfuse platelets, consider steroids, consider Pulm consult for bronch
- if c/f diffuse alveolar hemorrhage (see below), steroids

2) Consider pulmonary complications from the CA itself (best seen on chest CT):

a) **Tumor burden in parenchyma**
Tx: If obvious on imaging, no further intervention; rarely surgery

b) **Compression of airways from tumor**
Tx: Consider Interventional Pulm c/s for de-bulking or stent

c) **Lymphangitic spread (non-cardiogenic septal thickening)**
Etiology: presence of tumor in the pulmonary lymphatics and interstitium, causing thickened bronchovascular bundles and septal thickening
- Consider in RCC, HCC, and adenocarcinoma of breast, colon, lung, and stomach

W/u: If obvious imaging, no further intervention; can consider Pulm c/s for biopsies--transbronchial or surgical biopsies provide only definitive test but typically not pursued until all causes ruled out and if needed for staging
Tx: Treat underlying CA

d) **Pleural effusion**
Etiology: typically due to tumor on pleura but can also be 2/2 pneumonia (from bronchial obstruction), PE, or SVC syndrome
- Any malignancy, but common in lung, mesothelioma, breast, lymphoma, gyn
- Portends a poor prognosis (median survival ranges 1-12 mo. depending on associated CA); pH can be prognostically significant (**Ann Intern Med 1988;108:345**)(**Am Rev Respir Dis 1989;139:663**)

W/u: Thoracentesis w/ labs (including cytology)
Tx: Consult Pulm (thoracentesis only) vs Interventional Pulm (chest tube, PleurX, pleurodesis) vs Interventional Radiology (thora, PleurX--especially @ Newton Wellesley)
- Tx is ultimately palliative, w/ no survival benefit but can improve dyspnea; retrospective analysis of pts w/ pleural catheters showed 39% resolution of dyspnea (**Chest 2006;129:362**)

3) Consider pulmonary toxicities from treatment (best seen on CT):

a) **Pulmonary edema**
Etiology: Cardiogenic pulmonary edema vs capillary leak from chemo
- Clinically, can range from mild hypoxia to fulminant ARDS

W/u: Rule out cardiogenic edema first via EKG, TTE, cardiac markers
- Note: anthracyclines, cyclophosphamide, or chest XRT can cause this by affecting RV/LV function or simply increasing risk of ischemia + valvulopathy
- If not clearly cardiac, review Hx for taxanes (docetaxel can cause capillary leak), mitomycin C, vinblastine, ATRA, or IL-2 → please see table at end of chapter

Tx: Trial of diuresis if cardiogenic, consider steroids if noncardiogenic

b) **Pneumonitis**
Etiology: Heterogenous, but represents non-infectious inflammatory response (focal or diffuse) that may be the result of direct chemo toxicity, radiation, allergic reaction to chemo, or IRAE from checkpoint immunotherapy
W/u: Chest CT---can look like pneumonia, please r/o and treat for infxn first
- Indeed, consider if Tx'ed for pneumonia but not improving
- Review Hx for XRT to chest; certain chemotherapies (including MTX, bleomycin, etc. → please see table at end of chapter), checkpoint inhibitors
- Consider Pulm/Interventional Pulm c/s for biopsies vs. surgical biopsy (can be more confirmatory) vs. proceeding w/ steroids for tx

Side note on XRT-induced pneumonitis:
-appears 4-12 wks after completing XRT, but can also occur later
-often related to volume of lung receiving >20 Gy of XRT and may show up as pneumonitis in straight lines corresponding to region of XRT (w/o respecting anatomic borders)
-pts on ACEi may be higher risk, as are pts with underlying ILD
-consider "recall" radiation pneumonitis if later treated with carmustine, doxorubicin, etoposide, gefitinib, gemcitabine, paclitacel, or trastuzumab

Sidenote on checkpoint inhibitor pneumonitis (see IRAE chapter):
-meta-analysis suggests 2.7% overall incidence of pneumonitis for monotherapy vs 6.6% w/ combination therapy (dual-targeting of PD1/PD-L1 and CTLA4), w/higher incidence of PD1-inhibitor pneumonitis in NSCLC (~4%) and RCC (**JAMA Oncol 2016;2:1607**)
-for NSCLC, one study found ↑ incidence of pneumonitis w/ PD-1 inhibitor (nivo/pembro) vs PD-L1 inhibitor (atezolizumab, avelumab durvalumab); also, higher incidence in those Tx'ed w/immunotherapy as frontline tx (**Chest 2017;152:271**)

Tx: Steroids once infxn has been ruled out (may require high dose prednisone upfront w/ slow taper over wks; relapse is common); can consider steroid-sparing agents
Long-term f/u: consider PFTs, may warrant follow-up of lung volumes and DLCO over time as it can proceed to fibrosis

c) **Alveolar hemorrhage (as chemotoxicity)**
Etiology: drug toxicity, infection, heart failure, pulmonary embolism, ARDS--typically w/ abrupt onset (<7 days)

- histopath. can reflect pulmonary capillaritis, bland pulmonary hemorrhage, and diffuse alveolar damage-- distinct from "macro" causes of hemoptysis such as tumor invasion or PE.
- Note: hemoptysis NOT required for diagnosis, may be absent 1/3rd of the time
  W/u: chest CT showing diffuse b/l GGOs or consolidation (similar to pneumonitis)
- Review Hx for culprit chemo agents → please see table at end of chapter
- Formal diagnosis requires bronchoscopy (classically, serial BALs will be increasingly hemorrhagic)
- Consider Utox to assess for cocaine, UA to exclude pulmonary-renal syndromes
  Tx: Consider high-dose steroids

Chemotherapies with Direct Pulmonary Toxicity

Drug	Associated Pulmonary Clinical Syndromes
ATRA	Alveolar hemorrhage
Bevacizumab	Alveolar hemorrhage
Bleomycin	Eosinophilic PNA, hypersensitivity pneumonitis, interstitial pneumonitis, non-cardiogenic pulmonary edema, acute lung injury/ARDS, pulmonary veno-occlusive disease (PVOD)
Carboplatin	Acute bronchoconstriction
Carmustine	Radiation recall, PVOD
Cisplatin	PVOD
Crizotinib	Alveolar hemorrhage
Cyclophosphamide	Acute bronchoconstriction, interstitial pneumonitis, PVOD
Cytarabine	Hypersensitivity pneumonitis, non-cardiogenic pulmonary edema, acute lung injury/ARDS
Dactinomycin	Hypersensitivity pneumonitis
Docetaxel	Alveolar hemorrhage, capillary leak syndrome
Doxorubicin	Radiation recall
Erlotinib	Alveolar hemorrhage
Etoposide	Acute bronchoconstriction, alveolar hemorrhage, radiation recall
Fludarabine	Alveolar hemorrhage, eosinophilic PNA
Gefinitib	Alveolar hemorrhage, radiation recall
Gemcitabine	Alveolar hemorrhage, eosinophilic PNA, radiation recall, non-cardiogenic pulmonary edema, acute lung injury/ARDS, PVOD
IL-2	Non-cardiogenic pulmonary edema, acute lung injury/ARDS, capillary leak syndrome
Irinotecan	Alveolar hemorrhage
Lenalidomide	Alveolar hemorrhage, eosinophilic PNA
Methotrexate	Hypersensitivity pneumonitis, interstitial pneumonitis
Mitomycin	Interstitial pneumonitis, non-cardiogenic pulmonary edema, acute lung injury/ARDS, PVOD
Paclitaxel	Acute bronchoconstriction, radiation recall
Rituximab	Acute bronchoconstriction
Sorafenib	Alveolar hemorrhage
Sunitinib	Alveolar hemorrhage
Taxanes	Interstitial pneumonitis
TKI (dasatinib, imaginib)	Interstitial pneumonitis
Trastuzumab	Radiation recall
Vinorelbine	Acute bronchoconstriction

HSCT-Specific Pulmonary Complications

Allogeneic stem cell transplant (HSCT)-specific complications:

- Incidence: Occur in 20 to 40% of HSCT patients and cause significant morbidity and mortality (**Bone Marrow Transplant 2013;48:1224**)(**Biol Blood Marrow Transplant 2007;13:749**).

- Types of complications depend on time after transplant:
  - Early (< 1 month): DAH, Idiopathic Pneumonia Syndrome, pneumonia (bacterial, fungal, aspiration), pulmonary edema, engraftment syndrome, hyperacute GVHD
  - Intermediate (1-6 mo.): Drug pneumonitis
  - Late (> 6 mo.): Bronchiolitis obliterans, bronchitis from recurrent infections
  - Any time: GVHD, Infection (see Chapters 5 and 6 in this manual for more information)

- **Idiopathic pneumonia syndrome** (typically w/in 4 mo. of transplant)
  - Etiology: Capillary damage from high dose conditioning regimen → inappropriate donor immune cell activation.
  - Incidence: Up to 10% of all patients who receive a HSCT
    - pts receiving myeloablative chemo are 4x more likely to develop IPS as those receiving reduced intensity conditioning (8% versus 2% in one study) (**Blood 2003;102:2777**)
    - also a/w high-dose radiotherapy, high-dose cyclophosphamide and busulfan (**Int J Radiat Oncol Biol Phys 2005;63:876**)
  - W/u: Diagnosis requires meeting all 3 criteria:
    - Widespread alveolar injury ⟶ multifocal infiltrates on CXR or chest CT w/ Sx of pneumonia and impaired gas exchange
    - Absence of lower respiratory tract infection as excluded by bronchoscopy w/ BAL and preferably followed by repeat testing 2 wks later
    - Absence of left heart failure (TTE may be needed to exclude)
  - Tx: Typically high dose steroids (1 mg/kg of prednisone equivalent); biologic agents (including anti-TNFa) are under tx but not standard of care
  - Prognosis: rapidly progressive and carries a high mortality rate (up to 75% of patients die w/in 30 days of discharge from the hospital)

- **Bronchiolitis obliterans syndrome**-->3 mo. post-transplant
  - Etiology: Inflammation of small airways (bronchioles), causing airflow limitation and obstructive defect, typically w/o improvement after bronchodilators
  - Incidence: Most common late-stage complication of allo-HSCT (**Eur Respir J 2007;29:1007**); a/w chronic GVHD w/ 14% prevalence in these pts (**Biol Blood Marrow Transplant 2011;17:1072**)
    - risk factors include older age, MTX use, ABO incompatibility, low IgG, use of PBSC, FEV1/FVC<70% prior to transplant, and influenza/parainfluenza/RSV w/in first 100 days post-transplant (**Bone Marrow Transplant 2013;48:1224**)(**Am J Respir Crit Care Med 2003;168:208**)
  - Dx: PFTs (obstructive deficit) and high-res CT scan (ideally w/ insp and exp phases)
    - inspiratory phase with bronchiectasis and/or GGOs
    - expiratory phase will show mosaic GGOs or expiratory air trapping
    - Note: Diagnosis may be challenging as initial imaging may seem normal. Consider definitive diagnosis with open/VATS lung biopsy
  - Tx: Inhaled and systemic steroids
  - Prognosis: Can be poor—can lead to progressive and irreversible airflow obstruction +/- bronchiectasis (with associated recurrent infections)
    - in one study, lung function only improved in 8-20% of patients even with aggressive therapy with a mortality rate of 14-100% (median 65%) (**Eur Respir J 2007;29:1007**)
    - with underlying chronic GVHD, mortality rate of 40% at 10 yrs and w/o cGVHD, 18% at 10 yrs (**Am J Respir Crit Care Med 2003;168:208**)

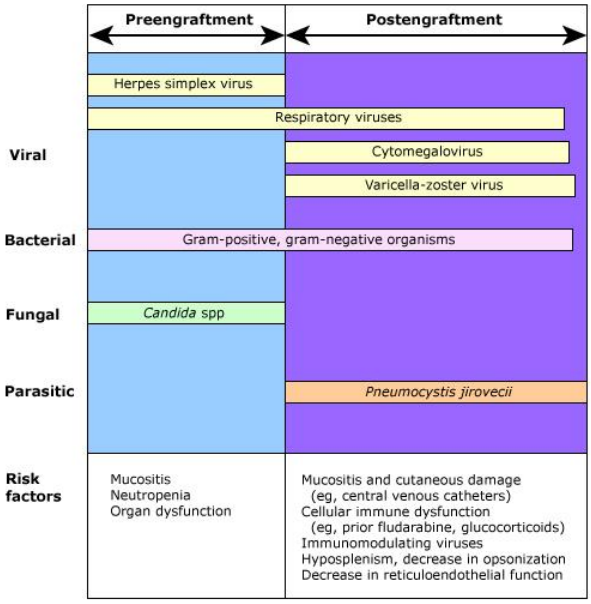
Autologous stem cell transplant-related toxicities:

- Similar complications occur with both allogeneic and autologous HCT, but allogeneic HCT requires more intense GVHD prevention with significant immunosuppression.
- With autologous transplants:
  - little to NO concern for GVHD, graft rejection
  - post-transplant CMV pneumonitis or Toxoplasmosis are very rare
  - early complications include: aspiration, edema, engraftment, DAH, chemo-induced
  - late complications include: restrictive PFTs, chronic lung toxicity, recurrence of heme malignancy or new primary malignancy

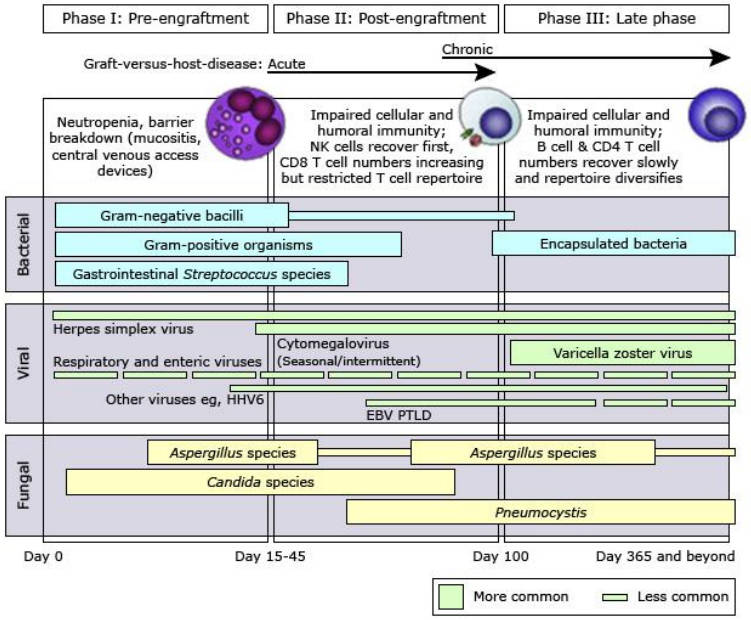
- **BCNU pneumonitis**:
  - Etiology: Attributed to oxidative stress, glutathione dysfunction, and immune-mediated injury from BCNU regimen
    - CBV regimen includes cyclophosphamide, BCNU, and etoposide
    - BEAM regimen includes lower dose BCNU, etoposide, cytarabine, and melphalan
  - Incidence: Variable, depending on study
    - retrospective study of risk factors found prior mediastinal RT, total BCNU dose >1000mg, and younger age to be a/w pneumonitis (Leuk Lymphoma 2012;53:1130), with threshold effect at doses of >1000 mg and incidence of 22%
    - may vary with regimen used--higher risk if receiving higher dose BCNU + whole body radiation rather than BEAM (Biol Blood Marrow Transplant); incidence of 4% with BEAM
  - Dx: Chest CT with pneumonitis as described above (again can range from hypoxemia to fulminant ARDS); may be a/w late-onset form of ILD called pleuroparenchymal fibroelastosis (PPFE) (Eur Respir J 2014;44:289)
  - Tx: Systemic high dose steroids

Opportunistic infections for auto- and allo-HSCT differ (graphics from Up-to-Date):

Timing of OIs for Autologous HSCT recipients on ppx:



Timing of OIs for Allogeneic HSCT recipients:



Approach to a Pulmonary Nodule

- Single or multifocal pulmonary nodular opacities are common findings in the oncology population, especially amongst patients with liquid tumors due to prolonged neutropenia.
- Nodules do not always need to be worked up but are concerning if they are newly seen on imaging (whether solitary nodules, nodules surrounding by GGOs—which may suggest inflammation) OR if clinical concern (fever, cough, dyspnea, hypoxia, leukopenia/leukocytosis)
- Differential includes:

Bacterial	Fungal	Other Infectious	Non-Infectious
GNRs (E. coli, PsA, Klebsiella) GPCs (Staph, Strep) Nocardia Burkholderia	Apergillus spp. Mucorales spp. Cryptococcus spp. Histo, Blasto, Cocci Pneumocystis	Tuberculosis NTB mycobacteria Viral (CMV)	Organizing Pneumonia Drug reactions Leukemia

Workup:

- BCx (at least one peripherally + off all line lumens if pt has indwelling line) cultures (off all line lumens if patient has one + at least one peripherally), UA, UCx, sputum Cx (gram stain + aerobic culture, fungal wet prep+ culture, AFB stain, modified AFB stain, mycobacterial culture, PJP), serum galactomannan, 1,3-BD glucan (n.b.: IVIG and IV albumin can cause false positives), LDH
- Consider sending serum Cryptococcal antigen, urine Histoplasma antigen (cross-reacts with Blastomyces, no need for additional testing), urine Coccidioidomycosis antigen
- Non-contrast chest CT is usually sufficient unless there is concern for abscess
- Consult ID for assistance with antimicrobial choice/duration; consult pulm for possible bronch w/ BAL, ?transbronchial Bx (w/in 24-48 hrs a/w improved micro yield and outcomes)

Tx: Empiric antibiotic tx depends on the duration of neutropenia and severity of illness:

- Neutropenia < 10d makes fungal infection less likely but not impossible: Start Vancomycin + Cefepime 2g q8h (redose if CrCl < 50). Consider Ambisome for fungal therapy.
- Neutropenia > 10d makes fungal infection more likely: Start Vancomycin + (Cefepime 2g q8h OR Meropenem 1g q8h) + Ambisome 5mg/kg q24h with pre-/post-hydration 250cc NS bolus.
    - In patients admitted overnight, single dose of Ambisome has benefit of covering most potential fungal pathogens and having very little renal toxicity (as this depends on cumulative dose), thus buying time to discuss case with ID.
    - NB: Meropenem may be chosen for coverage of Nocardia specifically (not just for drug-resistant GNRs); Nocardia will grow in sputum cultures, but you have to specifically request it in the "special requests" box of the culture order.
- If the patient has no clinical improvement after 5 days of antibiotics and antifungals, and cultures are negative, consider empiric steroids to treat organizing pneumonia (d/w pulm and ID)

Atrial Fibrillation

- **Risk Factors:** Conventional risk factors (age, comorbidities, inflammation), pleural/pericardial involvement, chemotherapeutic agents (ibrutinib associated with 4-fold increased risk), lung resection (predicted by elevated NT-proBNP/BNP 24-hours before or 1-hour after thoracic surgery)
- **Treatment**:
  - Rate/Rhythm Control: BB first-line, digoxin may be useful if GFR preserved, caution with CCBs (in setting of cardiotoxic chemotherapy EF depression), caution with amiodarone (QTc prolongation, drug-drug interactions, pulmonary/hepatic/thyroidal toxicity)
  - Anticoagulation: Patient-specific risk factor guided consideration of AC (CHA_2DS_2-VASc and HAS-BLED not validated but may be used to help guide risk estimates)
  - Traditionally warfarin/LMWH utilized, however, emerging data suggest safety/efficacy of DOACs (DOACs with signal for higher GIB so caution with use in luminal malignancies).
  - Caution: Beware of drug-drug interactions and increased risk of bleeding due to anti-platelet effects of some drugs and thrombocytopenia and anemia induced by many chemotherapeutic. INR is often more difficult to maintain in target range. No data supporting for catheter-based ablation, which comes with increased bleeding and thrombotic risk in cancer patients

LV Dysfunction

- **Risk Factors**: anthracycline use, thoracic radiation, pre-existing cardiomyopathy, CAD, arrhythmias, conventional risk factors (smoking, HTN, HLD, metabolic syndrome)
- **Prevention**: assessment of baseline cardiac function, optimize cardiac risk factors, avoid combination cardiotoxic therapy if possible (ex. doxorubicin + trastuzumab), cardioprotective delivery systems (liposomal doxorubicin), trial of ACE-I and BB in high-risk patients controversial
- **Treatment**: Early treatment recommended, standard HF GDMT is indicated, CRT/CRT-D therapy should be considered on case-by-case basis pending prognosis/GOC
- Classically described by two types of underyling mechanisms, but rapidly evolving given new data and drugs introduced.
  - Type I: dose dependent, leads to cell apoptosis, and irreversible at cellular level. Early detection and prompt treatment may prevent LV remodeling and HF. Example: anthracyclines
  - Type II: Not dose dependent and does not lead to apoptosis by itself so is often reversible. Example: trastuzumab

Thromboembolic Disease

- **Risk Factors**: Patient specific factors (advanced age, AA ethnicity, high BMI), high risk malignancies with aggressive metastatic potential (pancreatic, gastric, lymphoma etc.), thrombophilia, surgery/chemotherapy, acute hospitalization, central venous catheters, tumor related mass effect/vascular invasion
- **Risk stratification**: **Khorana-score** can be used to risk-stratify patients with solid tumors undergoing chemotherapy to guide decision regarding thromboprophylaxis (cannot be used in brain tumors/myeloma)
- **Prevention**: Consider thromboprophylaxis for high-risk patients (High Khorana Score, previous VTE) with LMWH, Multiple-myeloma treated with thalidomide/high-dose prednisone (low risk patients with ASA, high risk patients with LMWH)
- **Treatment**: Professional societies recommend at least 3-6 months of AC following cancer-associated-VTE. However, if active cancer, it is suggested to continue anticoagulation indefinitely for secondary prophylaxis (>6 months). Historically LMWH (over VKA) preferred, but with recent data of the efficacy/safety of DOACs, they are suggested as the initial and long-term treatment. Guidelines suggest treating subsegmental PEs

Arterial Toxicity

- **Risk Factors**: Raynaud's, certain chemotherapeutics (L-asparaginase, cisplatin, MTX, 5-FU, and paclitaxel), stroke risk increases with cervical/mediastinal XRT, increased carotid stiffness and advanced athero >10 years after XRT
- **Prevention**: Maintain good control of CAD risk factors, avoid use of highly toxic agents in known arterial disease (ex. avoid Niltonib in PAD)

ACS

- **Risk Factors**: Pre-existing CVD, thrombogenic cancers, pro-inflammatory state, chemotherapy induced vasospasm
- **Treatment**:
  - Do not hold ASA for thrombocytopenia

- Can safely use DAPT in patients with Plt>30-50K (but cannot use ticagrelor or prasugrel or GP IIb/IIIa inhibitors when Plt<50K)
- Heparin can be given when Plt<50K but using doses of 30-50U/kg for initial dosing
- No minimal Plt level is an absolute contraindication to coronary angiography
- In context of active ACS, coronary angiography +/- PCI can be guided by use of IVUS, FFR/iFR, or OCT to determine hemodynamic significance of lesions to weigh benefit of PCI versus OMT
- Optimal vascular access (femoral v. radial) is important (i.e. hx breast XRT/mastectomy, multiple previous arterial lines, chance of bleeding)
- CABG only for Plt>50K; patient must be reasonable candidate for sternotomy, stress of surgery
- Most cancer patients: increased risk of stent thrombosis when compared to patients without cancer and patients on chemotherapy have delayed stent re-endothelization
- Optimal duration of DAPT after ACS is typically minimally 2-4 weeks after PoBA, 1 month after BMS and 3-6 months after DES but is also dependent on numerous factors including presenting syndrome and need for anticoagulation
- If lack of clarity regarding DAPT continuation, ALWAYS SPEAK WITH A MEMBER OF THE CARDIOLOGY TEAM OR CONTACT INTERVENTIONAL CARDIOLOGIST WHO PERFORMED THE PROCEDURE: many factors play a role in decision to be more aggressive about DAPT continuation (stent type, diameter, length, drug that is eluted, location, involved/jailed side branches, PCI complexity, bifurcation stenting, evaluation of stent struts by intracoronary imaging, history of ISR/IST, extent of CAD, types of chemotherapy etc.)

Pericarditis

- **Risk Factors**: mediastinal tumors, metastases to the percardium, chemotherapy induced (cyclophosphamide, cytarabine, beomycin), XRT (can occur 2 mo – 15 years after)
- **Treatment**: NSAIDs, colchicine (possible marrow suppression, diarrhea, hypertension, CKD), prednisone

XRT-Induced Cardiovascular Disease (CVD)

- Increased risk (2- to 13-fold) of CVD in Hodgkin survivors and 2-fold in breast cancer patients
- XRT increases ischemic CAD (4- to 7-fold), valvular heart disease, interstitial myocardial fibrosis, CHF (diastolic dysfunction, restriction/constriction), constrictive pericarditis, conduction abnormalities (19-fold increased rate of PPM placement after chest XRT), malfunction of PPMs if neutron-producing XRT
- Risk Factors: age at exposure, total radiation dose (ex: >40Gy OR >30Gy AND anthracycline exposure), volume of tissue exposed, and lack of cardiac shielding techniques. Traditional risk factors (diabetes,etc.) also contribute to accelerated development of CAD and are important to aggressively manage.
- Most events 10-20 years s/p XRT; XRT-related cardiac disease usually manifests 15-20 years after initial treatment and CVD cumulative incidence is up to 50% at 40 years after initial treatment
- Pathophysiology: Poorly understood but causes epicardial AND microvascular disease via intimal hyperplasia, stenosis, atherosclerosis. Plaques are often long, smooth, more fibrotic with lower lipid burden.
- Radiation induced CAD often results in ostial or proximal lesions involving LM, proximal LAD, or RCA as these are areas more exposued to radation (anterior and central in mediastinum).
- XRT can cause atypical CAD presentations: possible silent ischemia (from concomitant neurotoxicity of XRT or chemotherapy affecting angina perception
- Screening for CAD: ASE/EACVI recommends functional non-invasive stress testing starting 10-15 years after initial cancer treatment for mediastinal XRT or TBI and continue lifelong q5yr or starting 5 years after if high risk (other CV RFs, >30 Gy, age>60)
- XRT also a/w valvular heart disease: fibrosis and calcification of the aortic root, aortic valve cusps, mitral annulus, base and mid-portions of mitral valve leaflets, sparing tips and commissures, distinguishing it from rheumatic heart disease
- XRT associated with a 9-fold increased risk of needing valvular surgery (median time = 22 years)
- Screening for valvular disease: ASE/EACVI recommends TTE 10 years post-XRT and serially q5y thereafter or 5 years post-XRT if high risk.
- XRT also increases cerebrovascular disease with 6-7% risk at 25 years for H&N and mantle XRT (or 2.2-5.6-fold increased risk of stroke), and 3-5-fold increased risk of CAD, 60% have ≥mild aortic regurgitation at 20 years
- Screening for cerebrovascular disease: if s/p XRT for H&N cancer/lymphoma: Carotid Duplex starting 5 years after XRT

Detection of Cardiotoxicity

- TTE (3D LVEF, 2D Simpson's EF): defined as >10% LVEF decrement to a value below LLN
- MUGA: >10% drop in LVEF to <50%; more reproducible than 2D TTE but more radiation exposure
- Cardiac MRI: Gold-standard for LVEF, also detects focal and diffuse myocardial fibrosis; accurate assessment of chamber volumes, RV/LV function, pericardium
- Biomarkers (TnI, hsTnI, BNP, NT-proBNP): a TnI rise identifies those receiving anthracyclines that may benefit from ACEi; BNP needs further investigation; Global Longitudinal Strain (GLS)>15% reduction from baseline (a TTE biomarker) is an early marker of risk and identifies those that may benefit from cardioprotective measures
- Do not switch between modalities unless the LVEF is borderline and the value has implications: otherwise, pick one and utilize trend to determine toxicity
- Cardiotoxic chemo recipients should have post-chemo LV function assessment once at 6-12 months (98% LV impairment detection rate in some studies) if there is increased risk defined as follows:
  - Doxorubicin > 250mg/m^2 or epirubicin >600mg/m^2 or >30Gy involving heart field
  - Doxorubicin<250mg/m^2 + XRT<30Gy OR epirubicin<600mg/m^2 + XRT<30Gy OR trastuzumab with ≥ 2 RFs: smoking, HTN, DM, HLD, obesity, ≥60 yrs, EF<50%, h/o MI, ≥mod. valvular disease
- Combo of biomarkers + GLS may predict future cardiotoxicity

Select Chemotherapeutics and their Cardiotoxicities

Anthracyclines

- Mechanisms of injury: Type 1. Topoisomerase-IIb inhibition in cardiomyocytes activating apoptotic pathway, RyR/SERCA inhibition (disrupted Ca^{2+} homeostasis), free radical/ROS damage, decreased autophagic flux, mitochondrial iron overload
- Risk Factors: high cumulative dose (250 mg/m^2), pre-existing CVD risk-factors (HLD, HTN, DM, obesity), pre-existing HFrEF, synergistic non-anthracyclines (trastuzumab, taxanes, XRT)
- Screening: Pre-chemo EKG + TTE, serial cardiac monitoring (at 6-12 months in high-risk patients or prior to each cycle), alternative screening tools include cMRI and MUGA
- Diagnosis: Made by endomyocardial biopsy
- Prevention: Avoid if HFrEF (EF <40%), optimal management of CVD risk factors, limit cumulative doses, liposomal preparation, infusion dosing over 48-96 hours vs. bolus, dexrazoxane (iron chelator) if cumulative anthracycline dose >250 mg/m^2, standard HFrEF management (ACEi/ARB/ARNI, BB, MRA, +/- CRT-D)
- Discontinuation:
  - If ΔLVEF>10% and LVEF<40%, symptomatic HF with LVEF decline
  - If asymptomatic decline to LVEF 40%-50%, or >15% reduction to LVEF<50%, define risk/benefit and assess alternative chemo, or if EF 40-50%, treat with ACEi/ARB+BB as many will progress to have further EF decline—notably, symptomatic HF with HFpEF (without LVEF decline) unlikely to be caused by anthracyclines
  - Must rule out alternative causes of new HFrEF (ischemic, myocarditis, infiltrative, stress/septic CMP, MI, differentiation syndrome with ATRA/AsO_3 in APML etc.)
- Prognosis: 11% have total EF recover, 71% have >5% improvement, and 18% have no recovery (associated with 10% 5 year cardiac death)

Fluoropyrimidines (5-FU, capecitabine)

- Risk factors: pre-existing CAD, infusion dosing (risk lower w/ bolus)
- Complications: angina, vasospasm, coronary artery thrombosis, arteritis, autoimmune response
- CV complications: endothelial injury, vasospasm, coronary artery thrombosis (3-7% with manifest MI, 7-10% silent MI), arteritis, autoimmune response, Takotsubo cardiomyopathy (trigger 2-4 week pause for BB, ACEi, EF recovery)
- Re-challenge: consent for possibility diffuse coronary vasospasm and death (pre-treat w/ CCB +/- nitrates); bolus dosing associated with less vasospasm compared to infusion dosing

Antimetabolites

- Cytarabine: pericarditis, effusion, and tamponade
- Fludarabine: hypotension, chest pain, cardiotoxic if combined with mephalan
- Gemcitabine: SVT, rarely cardiomyopathy
- MTX: rare SVT/VT, syncope, MI
- Pentostatin, cladaribine: rarely ischemia, CHF

Microtubule Inhibitors (Vinca alkaloids, taxanes)

- Vinca alkaloids (vinblastine > vincristine/vinorelbine): hypertension, MI
- Docetaxel: conduction abnormalities, cardiovascular collapse, angina/MI
- Eribulin: QTc prolongation
- Iaxebpilone: SVT, MI, ventricular dysfunction, possibly in combination w/ capecitabine
- Paclitaxel: bradycardia, CHB, sinus arrhythmias, cardiomyopathy if combined with doxorubicin, angina/MI

Alkylators

- Cisplatin: postural hypotension, SVT, bradycardia, LBBB, MI, ischemic cardiomyopathy, vascular toxicity (Raynaud's, hypertension, cerebral ischemic events), arterial thrombosis, large infusion volume leads to issues with volume overload in myocardial impairment. Electrolyte abnormalities assoc. w/ cisplatin nephrotoxicity may contribute to cardiac toxicities
- Cyclophosphamide: acute cardiomyopathy with high dose protocols, hemorrhagic myopericarditis with pericardial effusion/tamponade (can be rapidly fatal with death in 1st week of treatment)
- Ifosfamide: arrhythmias, CHF, ST-T wave changes
- Trabectedin: CHF, rare cardiac arrest

Anti-tumor Antibiotics

- Mitomycin: CHF, may be additive to anthracycline toxicity
- Bleomycin: pericarditis, angina, CAD/MI

Monoclonal Antibodies

- Aflibercept HTN, arterial thrombotic events
- Alemtuzumab CHF, arrhythmias
- Cetuximab CHF, increased risk of SCD/cardiopulmonary arrest if combined with XRT in 2%; if combined with platinum-based chemotherapy with 5-FU in 3% versus 2% with chemotherapy alone, therefore carries a black box warning for cardiopulmonary arrest and SCD; can induce a severe hypomagnesemia which possibly contributes to VF/SCD
- Ramucirumab HTN, arterial thrombotic events
- Rituximab rare arrhythmias, infusion-related MI, VF, cardiogenic shock
- Trastuzumab: CMP with decreased LVEF (6.2% at 1-year, 20.1% at 5-years), usually manifests during therapy, CMP usually reversible as cardiotoxicity due to changes in structure/functional changes in contractile proteins and mitochondria, rarely from cell death; 13.5% of patients require treatment interruption (30% due to CHF, 70% for asymptomatic LVEF decline)
    - If LVEF drops to <45% or >10% points from baseline to 45-49%, interrupt tx & start BB/ACEi, can reinitiate tx if LVEF>49%
    - Increased risk with anthracyclines, paclitaxel, or cyclophosphamide
    - Alternative HER-2 targeted therapies: lapatinib (2-5% cardiotoxicity at 4.5 years, 2-3% CHF), pertuzumab, T-DM1 have a similar toxicity profile

VEGF Inhibitors (NO inhibition, vascular rarefaction by reduction in # blood vessels, oxidative stress, thrombotic microangiopathy, nephrotoxicity; HTN intrinsic to mechanism and a marker of effectiveness)

- Bevacizumab: ischemic and arterial thrombotic events (3.8%), HTN, LV dysfunction (2%), CHF (1% with NYHA III/IV)
- Sorafenib: arterial thrombosis (1.7%), ACS (2.9% compared to 0.4% in placebo), ECG changes
- Sunitinib: arterial thrombosis (1.4%), CHF (8% with NYHA III/IV in those treated for GIST), ECG changes
- All three are associated with severe HTN (seen in 10-50%); >45% (high) risk of inducing new HTN or destabilizing previously controlled HTN (severe HTN in 2-20% of cases)
- HTN increased 7.5-fold, 6.1-fold, and 3.9-fold for bevacizumab, sorafenib, sunitinib, respectively
- Beware of concomitant use of steroids, NSAIDs, EPO, CYP3A4-meabolized cardiac meds which can increase [VEGFi] and exacerbate effects (i.e. diltiazem, verapamil)
- Can consider nebivolol which increases NO, or carvedilol
- All can induce multivessel coronary vasospasm (in 2.7-3%)

Topoisomerase inhibitors
- Etoposide: vasospastic angina, MI, QTc prolongation by hERG cross-inhibition, endothelial apoptosis

Immunomodulators
- IFNa: MI, atrial/ventricular arrhythmias, CHF
- IL-2: capillary leak syndrome (appearance of septic shock, partially fluid responsive also frequently requiring pressors, peaks 4h post-tx), MI, SVT/AF (9.7-17%), AF (4.3-8%), VT (0.4-1.1%),
- Lenalidomide: increases VTE and arterial thromboses, including MI and CVA in myeloma patients (<5% if monotherapy, 10-20% if combined with dexamethasone in Rd regimen)
- Thalidomide: a/w arterial and venous thrombosis, sinus node dysfunction, bradycardia (in 26-53%, resolves in 12-21 days), CHB

EGFR inhibitors
- Erlotinib (2.3% v. 1.2% gemcitabine developed acute MI, a/w 4-10% VTE) associated with 2.3% risk of multivessel coronary vasospasm

Differentiation agents
- Arsenic trioxide/AsO3: differentiation syndrome (can lead to pericardial effusions, tamponade, MI), QTc prolongation (26-93%, can last 8 weeks leading to increased risk of torsades des pointes: >500ms in >40% of patients, must be very careful in the first 24 hours), case reports of transient AV block requiring temporary pacing wire to continue tx
- ATRA: differentiation syndrome (can lead to pericardial effusions, tamponade, MI), 5-29% die from differentiation syndrome but less likely w/steroids

TKIs
- Alectinib: bradycardia in 8%
- Axitinib: HTN, arterial thrombotic events, LV dysfunction and CHF
- Bosutinib (QTc prolong.), osimertinib, pazopanib, lenvatinib, ponatinib: associated with SVT and AF
- Brigatinib: HoTN, bradycardia
- Ceritinib: sinus brady, QTc prolongation in 4% – caution with concomitant use of beta blockers if baseline HR<70bpm
- Cobimetinib, trametinib: CMP risk (esp. in cobimetinib combined w/ vemurafenib)
- Crizotinib: bradycardia (average 25 bpm decrease in HR, 31% with HR<50, QTc>500 or increase > 60ms in 1.3 and 3.5% of patients, respectively)
- Dasatinib: most commonly pleural and pericardial effusions (improve on withholding drug and re-introducing at lower dose ± steroids), CHF, a French trial showed it causes severe pulmonary HTN
- Ibrutinib: AF (3.86-fold increased risk), other SVTs, ventricular arrhythmias, CHF, conduction disorders, severe bleeding risk (caution with DOACs, warfarin)
- Imatinib: possible CHF risk
- Lapatinib: see trastuzumab above
- Nilotinib: QTc prolongation >500ms in <1%, 0.6% rate of SCD, black box warning
- Osimertinib: possible CHF and QTc prolongation
- Pazopanib, cabozantinib: a/w 2.69-fold increased risk of CHF with all VEGF TKIs compared to controls – no difference between TKI selective versus non-selective TKIs
- Regorafenib: HTN, MI; no CHF reported
- Ribociclib, selpercatinib, sorafenib, sunitinib, trametinib, vandetanib: QTc increases 14-35ms, up to >500ms (in 7-14%), TdP (0.09-0.16%), therefore, black box warning for QTc prolongation, TdP, SCD)
- Ripretinib: CHF
- Vandetanib: second highest incidence of QTc prolongation after arsenic trioxide (AsO_3), CHF
- Vemurafenib: QTc increase >60ms (in 5%), up to >500ms (in 1.5-2.9%)
- Zanubrutinib: AF, Aflutter

Proteasome Inhibitors (proteasome has important cardiomyocyte maintenance functions)
- Bortezomib: CHF (up to 4%)
- Carfilzomib: HTN, CHF (25%, it is a more potent proteasome inhibitor)
- CHF rates in trials ~5% versus 4% rate for dexamethasone (Richardson NEJM 2005)

HDACs
- Panobinostat: QTc prolongation (9-28%, black box warning for severe arrhythmias, EKG changes)
- Romidepsin: SCD, VT, QTc prolongation
- Vorinostat: PE (5.4% risk in clinical trials)

Immune checkpoint inhibitors (Increased risks when combinations of checkpoint inhibitors are used)
- Ipilimumab: immune-mediated myopericarditis (0.27% risk if combined with nivolumab)
- Nivolumab: AVB, rarely ventricular arrhythmias, myocarditis (0.06% myocarditis if monotherapy)
- Pembrolizumab: autoimmune myocarditis, sinus tachycardia, AF, SCD likely 2/2 autoimmune process
- Diagnosis and Treatment: check EKG, hsTnT, TTE, cMRI +/- biopsy; treat with high-dose steroids (methylprednisolone 1g/d) -> Add mycophenolate mofetil, infliximab, or ATG if no immediate response to steroids
- See **Section 9.6** of this manual for further discussions on myocarditis secondary to Immunotherapy

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Quick Resources

There are 4 main guidelines regarding immune checkpoint related adverse events: ESMO, SITC, ASCO, and NCCN. Refer to any of these for more information regarding nuances in irAEs.

Immune-Related Toxicities Quick Summary

Mechanism of Action (NEJM 2018;378:158)(NEJM 2016;375:1767)(Nat Rev Clin Oncol 2016;13:473)(Lancet Oncol 2020;21:294)

(i) cytotoxic T-lymphocyte antigen 4 (CTLA-4, targeted by ipilimumab),
(ii) programmed cell death 1 (PD-1, targeted by nivolumab,pembrolizumab, and cemiplimab)
(iii) programmed cell death ligand 1 (PD-L1, targeted by atezolizumab, avelumab, and durvalumab)

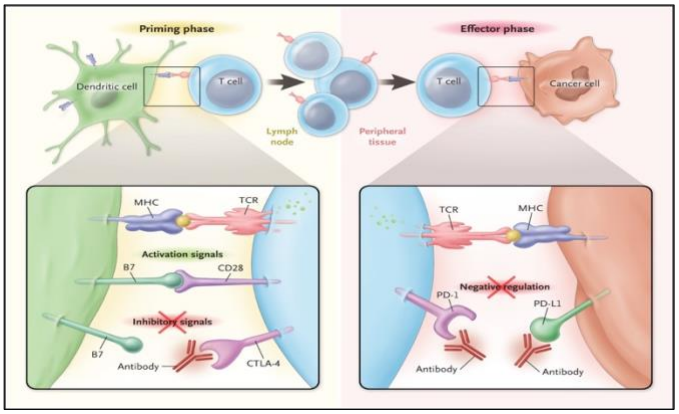
Most common Immune-related Adverse Events (irAEs) (UpToDate 2020)**:**

	Presentation	Work-Up	Treatment	Timing
Dermatology	Erythematous rash Vitiligo Mucositis	- Skin biopsy	- Steroids (topical or oral based on severity) - PO anti-pruritics	- 2-3 wks
GI	Colitis Diarrhea	- Stool culture - C. diff PCR - CMV PCR - EGD/colonoscopy	- Oral hydration - Steroids	- 6-8 wks
	Hepatitis	- AST/ALT - Bilirubin - CT abdomen/pelvis - Liver biopsy	- Steroids - MMF	- 6-8 wks
Pulmonary	Pneumonitis	- CT Chest	- Steroids	- Several mo. into tx
Cardiology	Myocarditis	- EKG, TTE - Troponin, BNP - CXR	- Steroids	- W/in 4 wks
Endocrinology	Hypophysitis	- Random cortisol, cort. stim., ACTH - Thyroid function tests - Brain MRI	- Steroids	
	Hypothyroidism	- Thyroid function tests	- Levothyroxine	
Rheumatology	Arthritis	- ANA, RF, CCP - ESR/CRP	- Acetaminophen & NSAIDs - Steroids	
	Myositis	- CK, AST/ALT - LDH, Aldolase - Troponin - ESR/CRP - EMG	- Acetaminophen & NSAIDs - Steroids	
Ophthalmology	Episcleritis Uveitis Conjunctivitis	- Fundoscopic exam - Neuro exam	- Topical steroids	

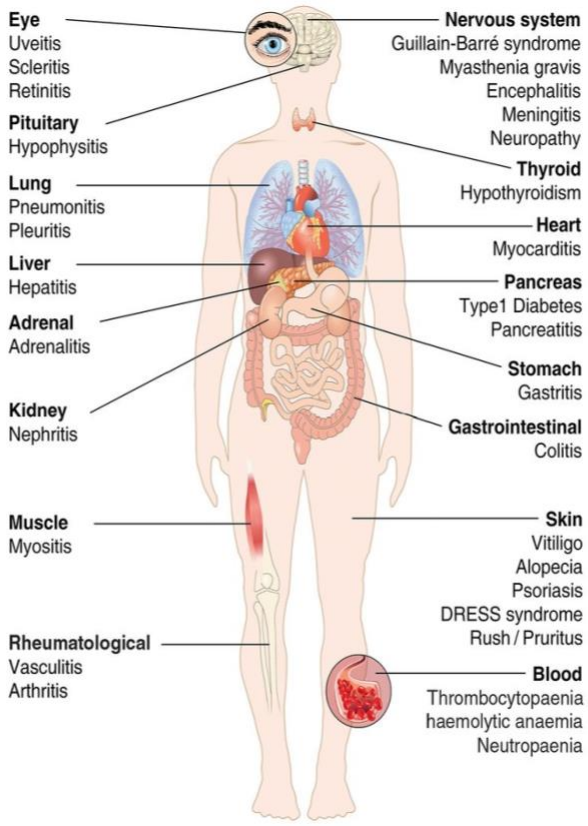
Immune Checkpoint Blockade: Mechanism of Action

Immune checkpoint inhibition (ICI) has revolutionized the tx of an ever-increasing spectrum of malignancies, w/ the hope of durable complete remission (CR) in a subset of patients w/ advanced or metastatic dz.

ICI attempts to increase antitumor immunity by blocking intrinsic down-regulators of the T cell response such as (i) cytotoxic T-lymphocyte antigen 4 (CTLA-4, targeted by ipilimumab), (ii) programmed cell death 1 (PD-1, targeted by nivolumab and pembrolizumab), or (iii) its ligand, programmed cell death ligand 1 (PD-L1, targeted by atezolizumab, avelumab, and durvalumab) (**NEJM 2018;378:158**) (**NEJM 2016; 375:1767**) (**Nat Rev Clin Oncol 2016;13:473**). Many other biologicals w/ similar mode of action (CD137, TIM-3, LAG-3) are in active development/ clinical trials (**Annu Rev Immunol 2016;34:539**).



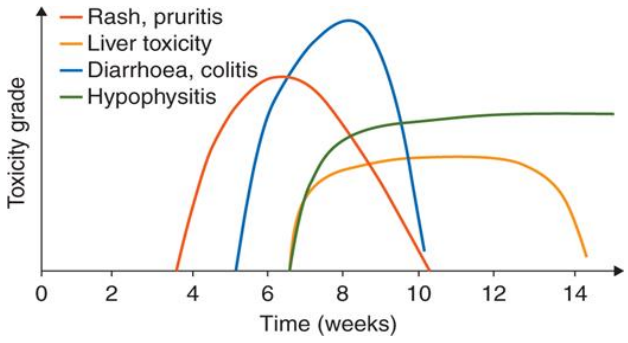
NEJM 2012; 366:2517-2519



Immune-related Adverse Events

The term irAE refers to autoimmune and other immune-mediated complications of ICI in the tx of CA (**NEJM 2018;378:158**). The spectrum of irAEs reported in the literature is still expanding and includes both organ-specific autoimmunity as well as systemic autoimmune dz. Combination immunotherapy (anti-CTLA-4 plus anti-PD-1) is a/w earlier occurrence, higher incidence, and often ↑ severity of irAEs(**J Immunother Cancer 2017;5:95**)(**JAMA Oncol 2016;2:1346**). We are unable to predict which patients will develop irAEs (**NEJM 2018;378:158**).

Timing of irAEs following anti-CTLA-4 therapy



Grading and Incidence of Immune-Related Adverse Events

Grading the severity of irAEs follows the NCI Common Terminology Criteria for Adverse Events (CTCAE), currently in its 5th iteration (2017). Grades 3 and 4 generally denote severe (but not immediately life-threating) and life-threatening adverse events (AE), respectively. Grade 5 indicates death related to the irAE and should warrant discussion of rapid autopsy. CTCAE grading for common irAEs is summarized in the table below. A complete list can be found at **https://safetyprofiler-ctep.nci.nih.gov/CTC/CTC.aspx**. Although uncommon, toxicities which develop from checkpoint inhibitors can become fatal, w/ myocarditis having the highest fatality rate (**JAMA Oncol 2018;4:1721**).

Grading of irAEs According to NIH/NCI Common Terminology Criteria for Adverse Events (CTCAE):

Organ System	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
General	Asymptomatic to mildly symptomatic, no intervention	Moderate, limiting ADLs, intervention indicated	Severe, but not immediately life-threatening; Hold ICI	Life-threatening; Discontinue ICI	Death related to specific AE Rapid Autopsy
Dermatitis	Macules/ papules/ bullae on <10% BSA	Macules/ papules/ bullae on 10-30% BSA	Macules/ papules/ bullae on >30% BSA	Life-threatening ICU or burn unit need	
Diarrhea	<4 stools/day above baseline	4-6 stools/day above baseline	>6 stools/day above baseline	Life-threatening	
Colitis	Asymptomatic	Abdominal pain, mucus or BRBPR	Severe abdominal pain, peritonitis	Life-threatening	
LFT abnl/ Hepatitis	ALT <2.5x ULN AST <3x ULN Bili <1.5x ULN AP <2.5x ULN	ALT 2.5-5.0x ULN AST 3-5x ULN Bili 1.5-3.0xULN AP 2.5-5.0x ULN	ALT 5-20x ULN AST 5-20x ULN Bili <3-10x ULN AP 5-20x ULN Asterixis, mild HE	ALT >20x ULN AST >20x ULN Bili >10x ULN AP >20x ULN HE and coma	
Pneumonitis (graded based on cough, SOB, hypoxemia)	SOB w/ moderate exertion No hypoxemia	SOB w/ minimal exertion SaO2 <88% w/ exercise	SOB w/ at rest SaO2 <88% or PaO2 <55 at rest	Life-threatening Need for intubation	
Myocarditis	Asymptomatic Troponin >ULN	Symptoms w/ exertion same EF 40-50% or 10-19% decrease	Symptoms at rest or minimal exertion Troponin c/w MI EF 20-39% or >20% decrease	Life-threatening same EF <20%	
Renal	Increased Cr x1.5 or >= 0.3 mg/dL	Increased Cr x2	Increased Cr x3 or Cr >= 4mg/dL (w/ acute rise of >=0.5mg/dL)	Receiving renal replacement therapy	

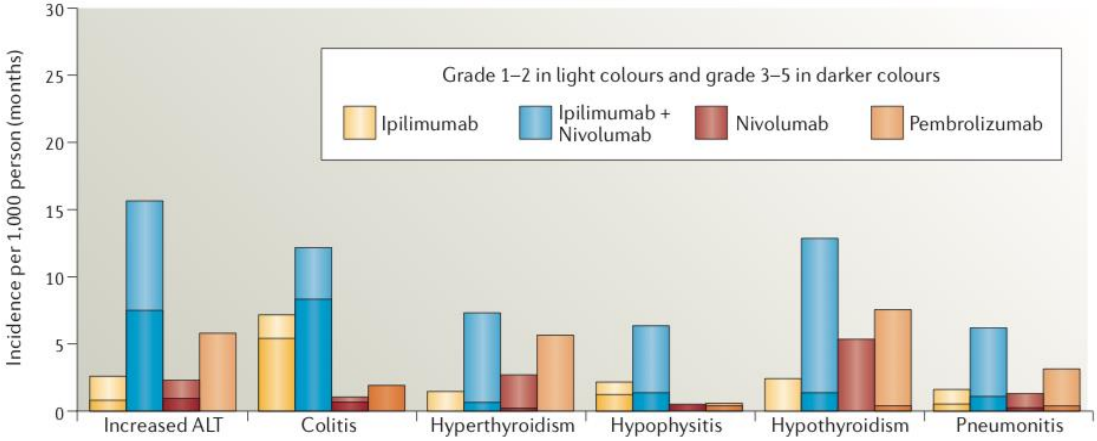
Who to Call: The Severe Immunotherapy Complication Service (SIC) is a dedicated consult service for patients admitted w/ suspected irAEs. Go to http://www.amion.com/ (Login: MGHCC) to find the covering oncologist. For subspecialty consultation related to irAEs: Dermatology (Steven Chen), Renal (Meghan Sise/ Yaa Oppong), Ophthalmology (Mary Aronow), GI (Michael Dougan/ Molly Thomas), Pulmonology (Robert Rogers/ Jason Maley), Cardiology (Tomas Neilan), Allergy (Aidan Long/ Jocelyn Farmer), Hematology (Rebecca Karp), Neuroendocrine (Alexander Faje), Neurology (Amanda Guidon), Rheumatology (Sara Schoenfeld/ Minna Kohler/ Mazen Nasrallah).

Prevalence of irAEs in Pts Treated w/ Ipilimumab, Nivolumab, or Combination Therapy (NEJM 2017;377:1345)

Table 2. Treatment-Related Adverse Events.*

Event	Nivolumab plus Ipilimumab (N=313)		Nivolumab (N=313)		Ipilimumab (N=311)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	300 (96)	184 (59)	270 (86)	67 (21)	268 (86)	86 (28)
Rash	93 (30)	10 (3)	72 (23)	1 (<1)	68 (22)	5 (2)
Pruritus	112 (35)	6 (2)	67 (21)	1 (<1)	113 (36)	1 (<1)
Vitiligo	28 (9)	0	29 (9)	1 (<1)	16 (5)	0
Maculopapular rash	38 (12)	6 (2)	15 (5)	2 (1)	38 (12)	1 (<1)
Fatigue	119 (38)	13 (4)	114 (36)	3 (1)	89 (29)	3 (1)
Asthenia	30 (10)	1 (<1)	25 (8)	1 (<1)	17 (5)	2 (1)
Pyrexia	60 (19)	2 (1)	21 (7)	0	21 (7)	1 (<1)
Diarrhea	142 (45)	29 (9)	67 (21)	9 (3)	105 (34)	18 (6)
Nausea	88 (28)	7 (2)	41 (13)	0	51 (16)	2 (1)
Vomiting	48 (15)	7 (2)	22 (7)	1 (<1)	24 (8)	1 (<1)
Abdominal pain	26 (8)	1 (<1)	18 (6)	0	28 (9)	2 (1)
Colitis	40 (13)	26 (8)	7 (2)	3 (1)	35 (11)	24 (8)
Headache	35 (11)	2 (1)	24 (8)	0	25 (8)	1 (<1)
Arthralgia	43 (14)	2 (1)	31 (10)	1 (<1)	22 (7)	0
Increased lipase level	44 (14)	34 (11)	27 (9)	14 (4)	18 (6)	12 (4)
Increased amylase level	26 (8)	9 (3)	20 (6)	6 (2)	15 (5)	4 (1)
Increased aspartate aminotransferase level	51 (16)	19 (6)	14 (4)	3 (1)	12 (4)	2 (1)
Increased alanine aminotransferase level	60 (19)	27 (9)	13 (4)	4 (1)	12 (4)	5 (2)
Decreased weight	19 (6)	0	10 (3)	0	4 (1)	1 (<1)
Hypothyroidism	53 (17)	1 (<1)	33 (11)	0	14 (5)	0
Hyperthyroidism	35 (11)	3 (1)	14 (4)	0	3 (1)	0
Hypophysitis	23 (7)	5 (2)	2 (1)	1 (<1)	12 (4)	5 (2)
Decreased appetite	60 (19)	4 (1)	36 (12)	0	41 (13)	1 (<1)
Cough	25 (8)	0	19 (6)	2 (1)	15 (5)	0
Dyspnea	36 (12)	3 (1)	19 (6)	1 (<1)	12 (4)	0
Pneumonitis	22 (7)	3 (1)	5 (2)	1 (<1)	5 (2)	1 (<1)
Treatment-related adverse event leading to discontinuation	123 (39)	95 (30)	37 (12)	24 (8)	49 (16)	43 (14)

Incidence of irAEs (Nat Rev Clin Oncol 2016;13:473)

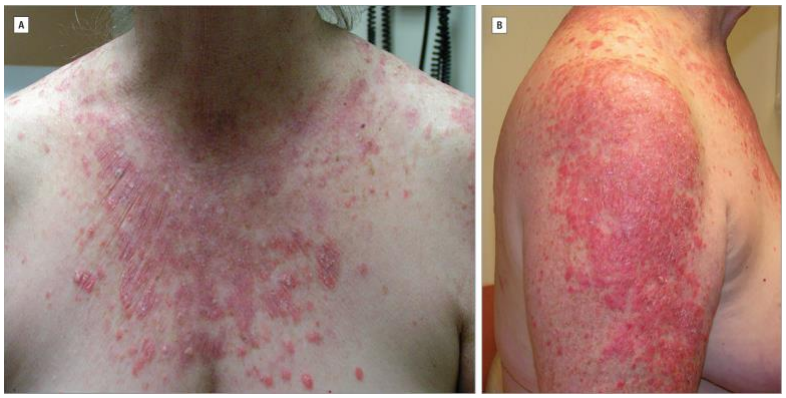


Organ-specific IrAEs

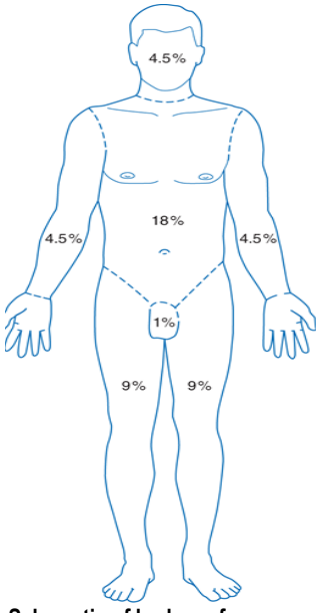
Disclaimer: No prospective trials have defined tx approaches to irAEs. Recommendations are based on consensus opinion (NEJM 2018;378:158)(J Immunother Cancer 2017;5:95)(J Immunother Cancer 2017;5:95), and glucocorticoids are usually the first-line agent. Despite concerns, oncological outcomes (progression free survival [PFS], overall survival [OS]) in patients w/ irAEs treated w/ immunosuppressive agents appear comparable.

Dermatitis/ Pruritus(J Immunother Cancer 2017;5:95)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)

- Skin is the most common organ system affected among irAEs; seen w/ both anti-CTLA-4 and anti-PD-1 (50% w/ ipilimumab; 40% of patients treated w/ aPD-1 [nivolumab or pembrolizumab] alone; 60% w/ combination immunotherapy). High grade toxicity is less common (<10%). Mucosal involvement is more commonly seen w/ aPD-1(JAMA Oncol 2016;2:1346)(ASCO Post 2013).
- Vitiligo is seen in 2-4% of pts treated w/ ipilimumab, irreversible



Grade 3 Cutaneous adverse events in a patient treated w/ pembrolizumab



Schematic of body surface area (BSA)

- Clinical Spectrum:
  - Commonly presenting as macules and erythematous, minimally scaly, pruritic papules that coalesce into plaques, most often involving trunk and extremities. Face and head are less frequently involved; palms and soles usually spared (JAMA Oncol 2016;2:1346)(ASCO Post 2013).
  - Mucositis/ Sicca syndrome
  - Autoimmune blistering dz, SJS/TEN, and Sweet's syndrome described
  - Melanocytes: vitiligo a/w improved outcomes in melanoma (JAMA Dermatol 2016;152:45).
- Timing: One of the earliest side effects (often w/in 2-4 wks of initiation), but can develop at any time (even after discontinuation of ICI)
- Dx: Evaluate all skin and mucosal surfaces (including conjunctiva); CBC diff (eosinophilia); consider skin biopsy; consider autoantibody testing if c/f autoimmune blistering dz; ANA, anti-Ro/La if c/f Sicca syndrome
- Tx:
  - Grade 1/2: treat w/ topical glucocorticoids
  - Grade 3: treat w/ oral glucocorticoids (usually at prednisone 1 mg/kg equivalent), +/- other immunosuppressants; hold ICI until symptoms resolve, permanent discontinuation must be considered
  - Grade 4 (SJS/TEN/bullous dermatitis, >30% BSA): dermatologic emergency, requires ICU/ burn level care, volume resuscitation, future ICI contraindicated
  - Pruritus (any grade): treat w/ systemic antihistamines, alcohol-free emollient creams, cold compresses, oatmeal baths, +/- topical glucocorticoids
  - Mucositis/ Sicca syn.: oral hygiene, magic mouthwash; artificial tears/ saliva

Colitis/Diarrhea (J Immunother Cancer 2017;5:95)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)(J Clin Oncol 2018;14:247)

- More commonly seen in anti-CTLA-4: incidence of Grade 3/4 colitis is higher w/ ipilimumab (8%) than w/ anti-PD-1 agents (1-2% w/ nivolumab or pembrolizumab). Combination therapy not a/w significantly higher Grade 3/4 colitis than ipilimumab alone (8% vs 8%).
  - Patients w/ ipilimumab-associated colitis may not have recurrence w/ nivolumab
- Clinical spectrum: Diarrhea most common presenting symptom, thought to be consequence of colitis. Prognosis is generally good, but fear perforation (1%).
- Timing: often 6-8 wks (median) after the initiation of therapy
- Dx: strict I/Os; CBC; BMP; CRP; ANCA; consult GI before giving any steroids for flex-sig or colonoscopy (esp. Grade 3/4)
  - Rule out alternative etiologies: Clostridium difficile PCR, consider other bacterial/viral pathogens (stool Cx, O&P, viral PCR, cryptosporidia), IgA anti-TTG
  - Imaging (CTAP) can show mild diffuse bowel thickening or segmental colitis a/w diverticulosis; Path differs from IBD and shows acute colitis
- Tx:
  - Symptomatic: Mild cases may be managed symptomatically w/ antidiarrheal agents after exclusion of infectious etiologies
  - Grade 1/2: can be treated symptomatically, treat w/ budesonide 9 mg PO or prednisone PO if fails to improve (G1>14d; G2>3d)
  - Grade 3/4: treat w/ systemic glucocorticoids (prednisone 1-2 mg/kg or methylprednisolone 1-2 mg/kg IV) w/ taper
  - Consider infliximab (anti-TNF) in refractory cases; consider MMF vs tacrolimus
  - IV fluids to compensate fluid losses; monitor for electrolyte abnormalities

Hepatitis/LFT abnormalities (Ann Oncol 2017;28(suppl_4):iv119)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)

- Hepatotoxic effects are observed in 4% of anti-CTLA-4 or anti-PD-1, but more frequently w/ combination therapy (16-19% w/ ipilimumab plus nivolumab)
- Beware that AST/ALT elevations >2:1 may indicate acute myocyte injury: The etiology of "LFT abnormalities" should be confirmed by checking CPK/aldolase. Myocarditis-myositis is a life-threatening complication of ICI a/w very poor prognosis.
- Clinical spectrum: often asymptomatic; RUQ pain, jaundice, N/V
- Timing: often 8-12 wks after initiation of ICI (wide range), earlier w/ combination therapy
- Dx: often first apparent as elevation of ALT/AST, occasionally Bili/AP elevation
  - Exclude viral and other drug-induced causes of hepatitis (hepatitis serologies; ANA, anti-SMA/LKM), consider RUQUS/Doppler for metastases/thrombus
  - Check hepatic synthetic function (albumin, INR, platelets)
  - Discuss liver biopsy in Grade 3/4 toxicity
  - Imaging is nonspecific, but can show periportal edema, hepatomegaly
- Tx: treat w/ glucocorticoids (prednisone 1-2 mg/kg/d or methylprednisolone 1 mg/kg/d if AST or ALT >400 or synthetic function impaired);
  - If dz steroids-refractory, consider MMF vs tacrolimus vs ATG
  - Infliximab is contraindicated in the tx of immune-related hepatitis
  - Grade 3: hold ICI and treat w/ glucocorticoids
  - Grade 4: permanently discontinue ICI; glucocorticoids

Pneumonitis (J Immunother Cancer 2017;5:95)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)(J Clin Oncol. 2017;35:709)(J Immunother Cancer 2020;8:e000840)

- Symptomatic pneumonitis is more common w/ anti-PD-1 (pembrolizumab> nivolumab), but serious toxicity is relatively rare. Combination immunotherapy confers significantly higher risk (see Fig. 4).
- Pneumonitis is discussed in detail under Pulmonary Side Effects of Cancer Therapy
- Clinical spectrum: cough, ↑ sputum production, SOB, DOE; life-threatening presentations as AIP/DAH are at the extreme of this spectrum
- Timing: Highly variable onset (9 days to 19 mo.), later than other irAEs
- Dx: (continuous) pulse ox, CXR, CT chest (PE protocol vs standard)
  - New: Consult pulmonology immediately for urgent bronch; do not start steroids before this

  - Workup DDX (viral and bacterial PNA, COP, heart failure, COPD exacerbation, lymphangitic carcinomatosis/ dz progression, PE): VBG, influenza/RSV PCR, extended viral panel, BCx, SpCx, sputum for PCP if at risk, consider BAL; NT-proBNP, troponin, consider TTE.
  - Imaging: radiographic appearance non-specific (GGOs, NSIP, COP-like, HP-like)
  - BAL notable for significant lymphocytosis (~30%)
  - Pathology often has findings of bronchiolitis obliterans organizing pneumonia
- Tx: oxygen supplementation, treat w/ glucocorticoids (prednisone 1-2 mg/kg/d or methylprednisolone) w/ prolonged taper, consider empiric abx, if appropriate, consider diuretics

Myocarditis (often in a/w Myositis) (J Immunother Cancer 2017;5:95)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)

- Rare, but serious adverse event of ICI a/w high mortality (33% cardiac death)
- Histologically characterized by T-cell infiltration of myocardium, no B cells or antibody deposits
- Myocarditis is discussed in detail under Cardiac Side Effects of Cancer Therapy
- Dx: EKG/ telemetry; hsTnT, NT-proBNP, ESR/CRP; TTE; consider myocardial Bx; CPK/aldolase; if c/f myositis, MRI/EMG/muscle Bx; Monitor for signs and symptoms of HF and AVB
- Tx:
  - Pulse-dose glucocorticoids w/ methylprednisolone 1000 mg IV daily x3-5 days; as second line consider infliximab (5 mg/kg); MMF, ATG (salvage);
  - Heart failure consult if reduced EF; beta-blockade; ACEi/ARB

Thyroiditis (Hypothyroidism/Hyperthyroidism) (J Immunother Cancer 2017;5:95)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)(J Clin Oncol 2018;14:247)

- Thyroiditis is more common w/ anti-PD-1/PD-L1 or combination w/ anti-CTLA-4
- Clinical spectrum: Thyroid involvement commonly presents w/ signs or symptoms of hypothyroidism (fatigue, cold intolerance, etc.), but may be preceded by periods of hyperthyroidism (release of thyroid hormone stores w/ gland inflammation)
- Dx: TSH, fT4/T4/T3 (check before every infusion); anti-thyroid antibodies (anti-TPO, anti-TG); make sure not to miss central hypothyroidism/hypophysitis in pts w/ low fT4 (TSH "abnormally normal")
- Tx:
  - If hypothyroid, start replacement w/ levothyroxine
  - If transiently hyperthyroid, treat w/ beta-blockers; methimazole is rarely needed; follow closely for hypothyroidism following period of hyperthyroidism

Hypophysitis (J Immunother Cancer 2017;5:95)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)(J Clin Endocrinol Metab 2014;99:4078)(J Clin Oncol 2018;14:247)

- Pituitary dysfunction is primarily seen w/ anti-CTLA-4 (ipilimumab) w/ an estimated prevalence of 10-12% (J Clin Endocrinol Metab 2014;99:4078). It rarely occurs w/ anti-PD-1/PD-L1 agents (<1%).
- Anti-CTLA-4: This entity may be mechanistically distinct from other organ-specific autoimmune irAEs and is thought to be mediated by direct binding and cytotoxicity of anti-CTLA-4 to CTLA-4 isoforms expressed on normal cells of the anterior pituitary (Sci Transl Med. 2014;6:230).
- Clinical spectrum (anti-CTLA-4):
  - Headaches (can be severe as in pituitary apoplexy) most common symptom (J Clin Endocrinol Metab 2014;99:4078).
  - Signs/symptoms of anterior hypopituitarism (hypocortisolism, hypothyroidism, hypogonadism, GH deficiency) include fatigue, N/V, dizziness, wt loss, hot flashes, cold intolerance, hypoNa (J Clin Endocrinol Metab 2014;99:4078).
  - Not a/w central diabetes insipidus (posterior pituitary/ ADH secretion spared) (J Clin Endocrinol Metab 2014;99:4078)
- Clinical spectrum (anti-PD-1/PD-L1): limited descriptions, institutional experience suggests that these patients present w/o significant headache or MRI changes and often are diagnosed w/ isolated central AI (Alex Faje, MGH)
- Timing: Median onset is 8 wks (J Clin Endocrinol Metab 2014;99:4078)
- Dx:
  - Imaging: MRI brain/pituitary protocol shows mild, transient (generally resolved by 2 mo.) and diffuse pituitary enlargement which can precede hormone deficiency

  - Testing hormonal axes: 8AM serum cortisol and ACTH and/or ACTH stimulation test; TSH w/ fT4/T4/T3 (inappropriately low TSH w/ low fT4); PRL levels; LH/FSH, serum testosterone and SHBG (in men); IGF-1 levels
  - Beware that concurrent primary thyroid dysfunction in patients also receiving anti-PD-1/PD-L1 agents can complicate thyroid test interpretation
- Tx:
  - Treat acutely w/ glucocorticoid replacement (high-dose does not improve outcomes)
  - Hypocortisolism: taper to physiologic glucocorticoid replacement doses (prednisone 3-5mg daily equivalent; increase x2-3 w/ infection/illness) and counsel about adrenal crisis/ stress dose glucocorticoids dosing; obtain medical bracelet
  - Hypothyroidism: thyroid hormone replacement w/ levothyroxine
  - Hypogonadism: consider testosterone replacement if persists
  - GH deficiency: GH contraindicated due to underlying malignancy (it is "growth hormone" for a reason)
  - Refer to MGH neuroendocrine unit for longitudinal follow-up
- Prognosis: Symptoms resolve w/ appropriate hormone substitution. The acute inflammatory process is non-recurrent, pituitary hormone deficiencies may be persistent (nearly all cases of central adrenal insufficiency).

Autoimmune diabetes mellitus(J Immunother Cancer 2017;5:95)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)
- De novo diabetes induced w/ ICI occurs at low frequency (<1%). DM appears to be more common w/ anti-PD-1/PD-L1 (or combination therapy) than w/ ipilimumab
- Dx: blood glucose, C-peptide and anti-GAD65, anti-islet cell (ICA) antibodies should be measured to distinguish between type 1 and type 2 DM; lipase
- Tx: Insulin; the role of glucocorticoids in preserving islet cell function is unclear so not generally used

Neurological toxicity(J Immunother Cancer 2017;5:95)(JAMA Oncol 2016;2:1346)(J Immunother Cancer 2017;5:95)
- Neuro-related irAEs occur in 4% of patients treated w/ anti-CTLA-4, 6% of anti-PD-1, and 12% of combination immunotherapy.
- Clinical spectrum: The spectrum of neurological irAE is broad and includes mononeuritis multiplex, mononeuropathies incl. facial neuropathy/ Bell's palsy, polyneuropathy, GBS-like dz, myasthenia gravis (MG), posterior reversible leukoencephalopathy, transverse myelitis (TM), encephalitis, aseptic meningitis (AsM), headaches, and ataxia.
- Timing: often 6-13 wks after initiation of therapy
- Dx: localizing neurological evaluation; workup depending on presentation
  - Consider ESR/CRP, MRI/MRA brain/spine, NCS/EMG, LP (cell count, Chem, viral PCR, smear/culture)
  - Appropriate dz-specific antibodies: anti-AChR /MuSK (MG), anti-GQ1b (Miller Fisher variant), ANCA (vasculitic neuropathy), ANA, autoimmune encephalitis panel incl. anti-NMDA (encephalitis)
  - Exclude non-irAE etiologies: neuropathy (prior chemo regimens/ alcohol/ meds, B12/folate, HIV, TSH, Hgb A1c, SPEP/ SFL); brain metastases (MRI); bacterial and viral meningitis/ encephalitis (LP); paraneoplastic encephalitis, seizure disorders (LTM); myositis (EMG, PFTs, MRI, CPK/aldolase)
  - Painful neuropathy is medium-vessel vasculitis until proven otherwise
- Tx: consult neurology early, do not forget about protecting the airway
- Concern for myositis and/or myasthenia prompts evaluation for myocarditis and thyroiditis (see also Myositis/ Neuromuscular dz)
  - if concern for GBS: IVIG or plasmapheresis, glucocorticoids
  - if concern for MG: pyridostigmine, glucocorticoids, IVIG or plasmapheresis; avoid medication that can precipitate myasthenic worsening
  - if concern for TM: glucocorticoids/ pulse-dose glucocorticoids
  - if concern for AsM: exclude viral/ bacterial causes; glucocorticoids; consider concurrent acyclovir and antibiotics until testing negative
  - if concern for nerve infarction/ vasculitis (foot drop, mononeuritis): do not delay empirical pulse-dose glucocorticoids

Systemic Autoimmune/Rheumatic irAEs

Arthritis (Ann Rheum Dis 2018;77:393)

- Arthritis a/w ICI has an estimated incidence of 1-7%; arthralgia is reported in >20% of patients and needs to be distinguished from frank arthritis.
- Clinical spectrum: The clinical presentation of ICI-associated arthritis can resemble
  - Rheumatoid arthritis (RA) w/ symmetrical polyarthritis of the PIPs, MCPs, and wrists (often anti-CCP/RF negative)
  - Reactive arthritis (ReA) w/ (oligo)arthritis, conjunctivitis, and urethritis
  - Seronegative spondyloarthropathies (SpA) w/ large joint oligoarthritis, axial involvement
  - Psoriatic arthritis (PsA)
  - polymyalgia rheumatica (PMR)
- Timing: often 6-13 wks after initiation of therapy, highly variable and can occur even after ICI has been discontinued
- Dx: Document tender and swollen joint; CBC diff, CRP/ESR, RF/anti-CCP (frequently negative), ANA/ anti-Ro/La, HLA-B27; if clinically indicated, synovial fluid analysis (cell count, cytology); plain films (baseline hands and feet), consider MRI/ MSKUS
- Tx: Tx may vary w/ arthritis phenotype. Consult rheumatologist early to expedite evaluation.
  - Non-inflammatory joint pain (arthralgias) can often be managed w/ NSAIDs, analgesics, and PT
  - RA-like dz: glucocorticoids, start w/ prednisone 20mg daily; may require higher doses of glucocorticoids than RA not a/w ICI (prednisone 1-2 mg/kg/day); consider HCQ, sulfasalazine, MTX, leflunomide; anti-TNF or anti-IL-6R (tocilizumab) in severe cases
  - ReA-like: glucocorticoids and infliximab
  - SpA-like: glucocorticoids (systemic or intraarticular), DMARDs (esp. sulfasalazine), consider anti-TNF therapy in severe cases/ the presence of other irAEs that warrant anti-TNF
  - PMR: glucocorticoids w/ prolonged taper

Myositis/ Neuromuscular disease

- Myositis can occur isolated or in combination w/ myocarditis. Myasthenia gravis as a consequence of ICI has also been described. These dz are rare and should prompt urgent interdisciplinary consultation (rheumatology and cardiology and/or neurology).
- Beware that myositis in a patient w/ active malignancy may be primarily driven by the CA (true DM/PM) or may represent a de novo irAE
- Clinical spectrum: Proximal LE/UE muscle weakness, myalgias may be present. Ocular weakness (ptosis/diplopia), dysphagia, facial, neck and respiratory weakness commonly involved.
- Dx: exam w/ focus on rashes in photosensitive distribution (shawl sign, holster sign), heliotrope rash, mechanic's hands, periungual erythema, Raynaud's phenomenon, joint exam; CPK/aldolase, AST/ALT, MRI muscle, EMG/NCS, consider muscle Bx, ANA/ anti-Ro/La, anti-Jo1, consider myositis panel 3; DDX includes NM dz such as myasthenia gravis: anti-AChR /MuSK, repetitive stimulation on EMG

Vasculitis

- Rare but potentially life-threatening irAE. Consult rheumatology for expedited workup.
- Dx: CBC diff, BMP, LFTs, ESR/CRP, UA/sediment, CXR, ANCA, ANA, anti-Ro, cryoglobulins (carry to lab at 37°C); if clinically indicated, bilateral TA Bx

Sicca syndrome (Sjogren's syndrome)

- Dry eyes and dry mouth (Sicca syndrome), may be underdiagnosed in patients treated w/ ICI
- Dx: ophthalmological exam (appropriate to consult MEEI optho), Schirmer test, ANA, anti-Ro/La

CAR-T Cell Therapy: Mechanism of Action

CAR-T cells are engineered T-lymphocytes. T cells are collected from the patient and genetically modified to express a chimeric antigen receptor (CAR), i.e. a fusion protein containing both an antigen recognition moiety and T-cell activation domains, that directs the cell to target a selected tumor antigen (CD19 CAR-T cell constructs are currently approved for the treatment of B-ALL and B-cell lymphoma)(**Nat Rev Clin Oncol 2018;15:47**)(**Blood 2016;127:3321**). For further discussions about CAR-T cell therapy indications, workflow, and clinical use, **see Section 5.3** of this manual.

Toxicities Associated with CAR-T Cell Therapy

CAR-T cells can cause toxicity by several mechanisms.

(1) "On-target, off-tumor toxicity": If the tumor-associated antigen targeted by the CAR-T cell is expressed on other (normal) tissues, those cells may be attacked (i.e. CAR-T cells targeting CD19 will deplete normal B cells).
(2) Cross-reactivity: CAR-T cells may cross-react with another protein not expressed on the cancer cell.
(3) Anaphylaxis and tumor lysis syndrome (TLS) following infusion of CAR-T cells. (See **Section 9.1** for further discussions on TLS.)
(4) Cytokine release syndrome (CRS): This is the most prominent toxicity of CAR-T cells. It refers to a syndrome of fever and hypotension that is caused by cytokines released by the infused CAR-T cells and/or their proliferation in vivo.
(5) CAR-T-cell-related encephalopathy syndrome (CRES): Neurologic toxicities due to CAR-T cell can occur with CRS (early) or in the absence of CRS (late).
(6) CAR-T-cell-related Hemophagocytic Lymphohistiocytosis (HLH): A profound unregulated, inflammatory state characterized by T cell hyperactivation; carries the worst prognosis (**Blood 2016;127:3321**).

Cytokine-release syndrome (CRS) (**Nat Rev Clin Oncol 2018;15:47**)

- Most common toxicity, usually within 1st week; fulminant cytokine release (IL-2, sIL2R, IFNγ, IL-6, GM-CSF) triggered by CAR-T engagement of cognate antigen/proliferation. Increased risk in bulky disease and with specific constructs.
- Signs/Symptoms: fever, malaise, anorexia, myalgia, hypotension, can affect any organ system (CV, lung, GI, liver, renal, CNS).
- Diagnosis: monitor for at least 7 days after CAR-T infusion: basic labs, ferritin, CRP, TLS labs; telemetry. As always, it's imperative to exclude infection.
- Therapy: Grading system (grade 1-4) based on organ system
  - Empiric broad-spectrum antibiotics if febrile
  - Tocilizumab (anti-IL6R) or siltuximab (anti-IL6) are drugs of choice for the management of CRS: can induce rapid reversal
  - Generally avoid glucocorticoids in order to prevent CAR-T failure (should discuss with primary oncologist first)
  - Many patients with CRS will require ICU level supportive management; transfer early
    - Marjority: high-dose pressers; minority: ventilation, CRRT, plasma exchange
- See Figure below for CRS toxicities that affect a variety of organ systems

CAR-T-cell-related encephalopathy syndrome (CRES) (**Nat Rev Clin Oncol 2018;15:47**)

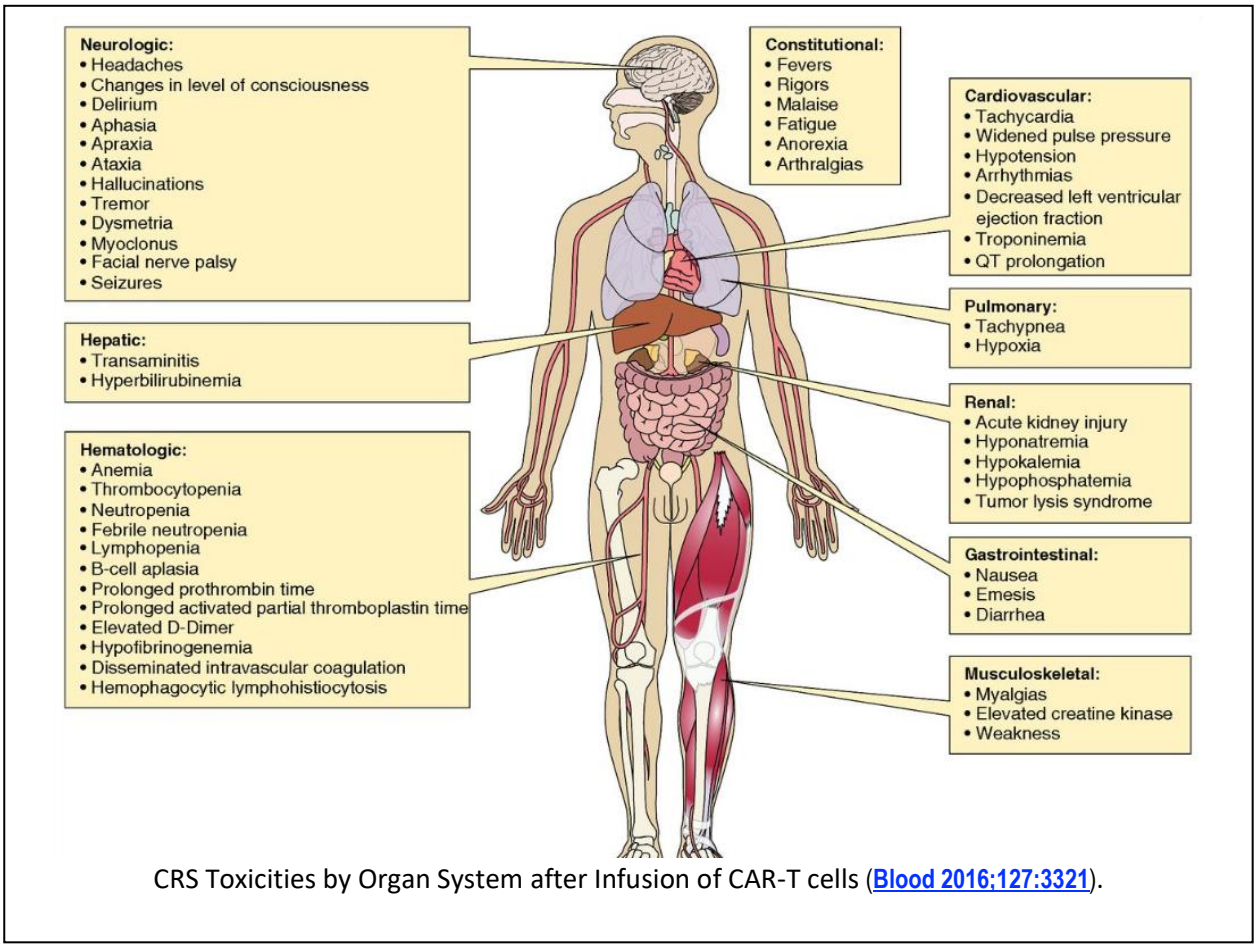
- Etiology is unclear; passive diffusion of cytokines into brain (IL-6, IL-15 a/w neurotoxicity) and/or trafficking of CAR-T into CNS have been implicated in CRES.
- Timing/Duration: typically lasts for 2-4 days, but can vary in duration from hours to weeks.
  - Can have biphasic presentation: 1st phase w/ fever and CRS (first 5 days); 2nd phase after fever/CRS subsided; delayed neurotoxicity/seizures in 10% (3-4 weeks after transfusion)
  - CRES a/w CRS generally of shorter duration, lower grade (grade 1-2) than post-CRS CRES (>3, protracted)
- Signs/Symptoms: typically manifests as toxic encephalopathy.
  - Earliest signs: diminished attention, language disturbance, impaired handwriting
  - Other manifestations: AMS, agitation, somnolence, aphasia, tremors
  - Severe CRES (grade >2): seizures, motor weakness, incontinence, increased ICP, papilledema, cerebral edema
- Diagnosis: Neuro consultation generally recommended; compute CARTOX-10 score; spot EEG (epileptiform/ diffuse generalized slowing); funduscopic exam; MRI brain w/wo contrast (usually negative) > CT; LP w/ opening pressure, CSF studies (typically with increased protein, can find CAR-Ts in CSF, rule out infection).
- Therapy: General: seizure ppx with levetiracetam for 30d; consider ICU transfer (>grade 2)/ airway protection (gr 4).
  - 1st phase (a/w CRS): anti-IL-6 (tocilizumab/ siltuximab) can reverse CRES; glucocorticoids if refractory or grade 2 (always confer with oncologist)

- 2nd phase (post-CRS): anti-IL-6 generally ineffective (less permeability of BBB post CRS?); glucocorticoids preferred
- If cerebral edema: acetazolamide, glucocorticoids; HOB>30; hyperventilate to P_aCO_2 30mmHg; mannitol; consult NSGY if significant edema

- Prognosis: CRES is generally reversible, rare fatal cases.

CAR-T-cell-related hemophagocytic lymphohistiocytosis (HLH)/ MAS (**Nat Rev Clin Oncol 2018;15:47**)

- Profound systemic inflammatory state characterized by CTL hyperactivation (IFNγ)→ macrophages (IL-6), lymphohistiocytic tissue infiltration, and multiorgan failure; ~1% of patients treated with CAR-T.
- Definition (proposed): Patient with peak ferritin >10,000 during CRS phase (typically <D5), and two of the following: grade ≥3 organ toxicities involving the liver, kidney, lung; or hemophagocytosis in bone marrow/ other organs.
- Signs/symptoms: Fever, cytopenias (2/3 lines); signs and symptoms related to multi-organ dysfunction
- Diagnosis: laboratory findings resemble HLH; CBC diff (cytopenias), ferritin (>10,000), soluble IL2R, LDH, fibrinogen, triglycerides, AST/ALT, Bili, Cr; BMBx rarely critical (low sensitivity, low specificity).
- Therapy: High mortality, do not delay diagnosis, escalate therapy aggressively.
  - Manage with anti-IL-6 (tocilizumab) and high-dose glucocorticoids; commonly necessitates additional therapy.
  - If fails to improve in 48h, consider etoposide as in HLH-94 treatment protocol and intrathecal cytarabine.



CRS Toxicities by Organ System after Infusion of CAR-T cells (**Blood 2016;127:3321**).

Basic Pain Control Algorithm and High-Yield Facts:

Tylenol 650-975mg q6hrs PRN
(650mg q8h PRN if ESLD)

⬇

Tylenol 975mg q6-8h scheduled
(650mg q8h if ESLD)

⬇

Ibuprofen 600mg q8h PRN or Toradol
15mg IV q6h PRN
(avoid if AKI, CKD or bleeding risk)

⬇

Additional considerations by etiology:

- If localized: topicals (lidocaine patch, voltaren gel, capsaicin cream)
- If localized to metastases: Rad Onc consult for palliative RT
- If localized to nerve/nerve plexus: pain consult for nerve block
- If bone: topicals, bisphosphonates (caution in multiple myeloma) or steroids (caution, can affect diagnostic yield of heme malignancy biopsies and interfere with immunotherapies/CAR-T)
- If muscle: topicals, baclofen, tizanidine, cyclobenzaprine
- If neuropathic: SNRI (duloxetine preferred), gabapentin/pregabalin, TCA's, clonidine
- If on methadone or buprenorphine for OUD, consult ACT or Palliative Care for assistance with dosing as these can be used for pain control as well

⬇

Opioid therapy:

- Order concurrent scheduled senna 2 tabs QHS or polyethylene glycol 17g daily
- If switching opioids, reduce equianalgesic dose of new opioid 25%-50% for incomplete cross tolerance
- If pain not controlled, increase opioid dose 50% if RR >12 and no altered mental status

↙ ↘

Opioid naïve:

Oxycodone IR, 2.5-5mg q4h prn
if no AKI or CKD

⬇

Oxycontin, 24hr need of Oxycodone split into
BID dosing plus 10-20% rescue dose for breakthrough

⬇

Hydromorphone 1-2mg PO q4hrs prn
Hydromorphone 0.25-0.5mg IV q4hrs prn as breakthrough

⬇

If requiring meds more than q2hrs, or sudden uncontrolled breakthrough pain, consider PCA +/- palliative care consult

Opioid tolerant or on opioids at home:

1. Re-order home/prior opioids, methadone/buprenorphine, or dose equivalent
2. Switch oxycodone/contin and morphine/MScontin to hydromorphone if AKI

⬇

Increase dose of home opioid as needed or switch to equianalgesic hydromorphone for acute pain crisis

Opioid Equianalgesic Doses		
Drug	PO (mg)	IV (mg)
Morphine	30	10
Oxycodone	20	n/a
Hydromorphone	7.5	1.5

Pain crisis management:
Goal is reduction in pain score by >50%.

1) Opioid-naïve: provide hydromorphone IV 0.25-0.5 mg bolus dose
   Opioid-tolerant: convert usual breakthrough PO dose or 10-20% of total daily ER dose to IV and administer
2) Assess for response after 15 min
   No pain relief and no side effects → increase dose by 50-100%
   Minimal relief and no side effects (<50% reduction in pain score) → repeat the same dose
   Pain reduced >50% and no side effects → reassess in 2-3 hours, use this dose as new breakthrough
   Side effects with no pain relief → rotate to different IV opioid (no dose reduction if uncontrolled pain)

Pathophysiology of Pain (Lancet 1992;339:1026, Dis Mon 2016;62:324)
Distinguish nocioception (nervous system activation by potentially tissue-damaging stimuli) vs pain (the perception of nocioception) vs suffering (the "total pain" experienced, or the threat to the status of the patient as a whole person).

1) Nociceptive: Tissue injury activates 1° afferent neurons (nociceptors) in skin, muscle, joints, visceral organs.
   - Visceral (hollow viscus, organ capsules, myocardium): gnawing, crampy, aching, throbbing
   - Somatic (bones, joints, muscles): aching, stabbing, throbbing, pressure-like
2) Neuropathic: Aberrant somatosensory processing produces pain due to dysfunction in the central or peripheral/autonomic nervous system.
3) Idiopathic: Nocioceptive or neuropathic factors have not been identified to adequately explain patient's pain. Includes functional pain syndromes and "psychogenic" pain.

Types of Cancer Pain (J Pain Sympt Manage 1996;12:273, Pain 2019;160:19, Hem Oncol Clin N Am 2018;32:371)
Antineoplastic Therapy-Related Pain: Side effects from chemo, immunotherapy, hormonal therapy, and RT:

- Mucositis
- Neuropathies
- Radiation-induced: cystitis, enteritis, proctitis, myelopathy, osteoradionecrosis, and others
- Arthralgias
- Myalgias
- Angina
- Bone pain
- Flare syndrome (bone pain & possible cord compression a/w LHRH agonist for prostate cancer)
- Palmar-plantar erythrodysesthesia (painful rash on palms and soles)
- Post-surgical pain (i.e. mastectomy, thoracotomy, pelvic surgeries)
- Phantom limb pain
- Lymphedema

Malignancy-Related Pain

- Bone metastases
- Vertebral syndromes
- Soft tissue or visceral metastases
- Leptomeningeal metastases
- Epidural spinal cord compression
- Malignant bowel obstruction
- Pathologic fracture
- Tumor hemorrhage
- Tumor-related neuropathic pain

Other

- Immobility
- Constipation
- Thrombophlebitis, DVT, PE

Pain Management:

NON-OPIOID ANALGESICS AND INTERVENTIONS:
Opioid-sparing therapies should be used whenever possible, keeping in mind etiology and severity of pain, as well as goals of care. Options include: (1) Non-Pharmacologic Options, (2) Nociceptive Pain Agents, (3) Neurogenic Pain Agents, (4) Steroids, (5) Topicals/Blocks for Regional Nerve/MSK Pain, or (6) Palliative Chemo/RT

Non-Opioid Pharmacologic Agents			
Medication	**Examples**	**Type of Pain**	**Notes/Toxicities**
Acetaminophen	Acetaminophen (Tylenol) 650-975 mg q4-6h IV or PO (max dose: 3-4g QD, ESLD 2g QD)	Mild to moderate	Liver toxicity; No evidence of effect on neuropathic pain
NSAIDs	Ibuprofen (Advil, Motrin) 400–600mg q6h (max dose: 2400mg QD) Naproxen 250-500mg q8-12h (max dose: 1g QD) Celecoxib (Celebrex, COX-2 select) 400mg load, then 200mg BID Ketorolac (Toradol) 15-30mg IV q6h	MSK, bone pain	Renal toxicity Bleeding risk (less GI bleed risk with Celebrex) CV risk

Steroids*	Dexamethasone 4-8mg PO 2-3x/day Methylprednisone 16-32mg PO 2-3x/day Prednisone 20-30mg PO 2-3x/day	Bone pain	HTN, Cushing's, wt gain, PUD, DM, insomnia, anxiety, skin thinning, immunosuppression*, leukocytosis, osteoporosis
Muscle relaxants	Baclofen 5g PO TID (starting dose) Tizanidine 4mg PO TID (starting dose) Cyclobenzaprine 5mg PO TID (starting dose)	MSK	Drowsiness, may need to taper over 1-2 wks
Topicals	Topical lidocaine 2-5%, Lidoderm patch 4% (1-3 patches 12h/day), capsaicin cream (QID) or patch (1-4 patches x30-60 min q3 months), diclofenac (Voltaren) gel or patch, methyl salicylate-menthol ointment (3-4x/day)	MSK Neuropathic	Erythema, petechiae, pruritis, dermatitis, pain exacerbation, xeroderma, desquamation (diclofenac)
Bisphosphonates**	Zoledronate 4mg IV; frequency depends on malignancy type. Admin over 15 min (or 30-45 min for multiple myeloma). Pamidronate 90mg IV q4wks. Admin over 2 hrs.	Bone pain	Check Vit D & replete prior to dosing; Renal toxicity; Jaw osteonecrosis; Fever/myalgias

Adapted from BWH Pink Book on Pain Management; MGH White Book; NEJM 2019 380:2440.
*Can affect therapeutic efficacy of therapies (especially immunotherapy, CAR-T), as well as diagnostic accuracy of biopsies (particularly for heme-based malignancies). Discuss w/ onc attending +/- pharmacy prior to prescribing.
**Caution in Multiple Myeloma patients as degree of renal impairment from elevated serum immunoglobulins can predispose to tx + dz related renal tox

Non-Opioid Analgesics for Neuropathic Pain					
Medication	**Starting dose**	**Uptitration**	**Max Dose**	**Metabolism**	**Notes**
Gabapentin	100-300mg TID	100mg TID	1200mg TID	Adjust for GFR	slow taper to d/c; risk for misuse and dependence
Pregabalin	75mg BID	25-150mg/day at weekly intervals	300mg BID	Adjust for GFR	slow taper to d/c
SNRI: Duloxetine	30mg QD	30mg q7d	60mg BID	Hepatic clearance	HTN; Withdrawal w/ abrupt discontinuation
TCA: Amitryptaline, Nortriptiline	10-25mg QHS 10-25mg QHS	10-25mg q7d 10-25mg q3d	75mg BID 150mg/day (divided doses)	Hepatic clearance Monitor QTc	Beware in elderly; CV risk; delirium; withdrawal w/ abrupt discontinuation

Adapted from the MGH White Book, NEJM 2019 380:2440.

REGIONAL PAIN TREATMENT OPTIONS:

1. Topical analgesics (lidocaine patches, voltaren gel)
2. Nerve Blocks: Consult the inpatient pain service.
    a. Celiac plexus block is often helpful for abdominal pain d/t pancreatic CA.
3. Epidurals: Consult the inpatient pain service.

PALLIATIVE CHEMO/RT:

Defined as chemo/RT used for symptom management (e.g. relieve tumor burden), not expected to be curative.

- In general, for palliative RT, patients who have localized symptoms from limited numbers of targetable neoplastic sites are good candidates. This not only includes pain from bone mets, but also symptoms such as hematuria/bleeding from prostate/GYN CA, neurological deficits from brain mets, or SVC syndrome from mass in R lung.
- When disease burden is diffuse, palliative chemo is typically preferred.
- Radiopharmaceutical therapy is a palliative tx which delivers localized radiation to areas of osteoblastic mets by injection.

OPIOIDS:

Opioids do not have a maximum pharmacological dose. Dosing may be limited by side effects, such as somnolence, decreased respiratory effort, or hypotension. The ideal dose controls pain with the fewest side effects while optimizing functional status.

Patients using long-acting opioids may still require short-acting opioids for breakthrough pain. Opioid combination products, consisting of an opioid and either acetaminophen, aspirin, or ibuprofen, are used for moderate episodic pain (e.g. breakthrough) on a PRN basis. The non-opioid component limits the dose of the opioid combination product.

Commonly Used Opioids							
Agonist	**Class**	**Mechanism**	**Route**	**Onset (min)**	**Peak Effect (min)**	**Dur. of effect (h)**	**Equi-analgesic Dosing***
Morphine	Natural	1°: μ agonist 2°:κ/δ agonist	PO	15-60	90-120	4	30
			IV	5-10	10-30	3-5	10
Hydrocodone (Codeine)		μ agonist Lower affinity δ	PO	30	90	3-4	20
			--	--	--	--	n/a
Oxycodone	Semi-synthetic	μ agonist Lower affinity κ/δ	PO	15-30	30-60	4-6	20
			--	--	--	--	n/a
Hydromorphone (Dilaudid)		μ agonist	PO	15-30	90-120	4-6	7.5
			IV	5-20	15-30	3-4	1.5
Methadone†	Synthetic	μ agonist NMDA antagonist	PO	30-60	90-120	4-12**	--
			IV	10-20	60-120	4-6	--
Fentanyl‡		μ agonist (lipophilic, ++CNS)	SC	--	--	48-72	--
			IV	< 1	5-7	.75 – 2+	0.1 (100mcg)

Adapted from BWH Pink Book on Pain Management & MGH White Book

* If converting across opioid classes, dose-reduce by 25-50% to account for incomplete cross-tolerance.

** Terminal half-life of methadone ranges 6–150h, while analgesic effect lasts for 4-12h with chronic dosing.

†Methadone cannot be converted linearly from other opioids.

‡ Transdermal fentanyl releases from subcutaneous fat. After patch is removed, fentanyl will remain in the system for 6-18h.

Opioid Conversion:

Step 1: Calculate equivalent ("equianalgesic") 24hr opioid dose of the desired opioid using the table above.

Step 2: Reduce calculated 24hr dose by 25-50% due to incomplete cross-tolerance

Step 3: Divide calculated dose by number of doses per day
Step 4: Order liberal "rescue" dose (10-20% of 24h starting dose)
Step 5: Recalculate scheduled dose based on patient response after 24-48h, consider long-acting formulations

Opioid Dosing:

- To assess efficacy of pain control, always ask "how much does the dose reduce the pain" (from # out of 10 to # out of 10) and "how long does the pain relief last"?
- In general, if the pain is not reduced enough, you need a higher dose. If the pain relief does not last, you need more frequent dosing. If both are issues, increase the dose alone first and re-assess.
- If a patient requires a significant amount of opioids throughout the day and particularly at night (e.g. frequently woken from sleep with pain) AND the pain is likely to continue for more than a few days, consider long-acting agents / infusions.
    - Infusions can take up to 24h to reach max effect and should generally be increased no more than 1x/d for safety.

Patient-Controlled Analgesia (PCA):

Consider consulting Palliative Care for an oncology patient transitioning to PCA.

1. PCA may be used in patients requiring IV opioids provided that the patient is alert, oriented, not delirious, and able to use the equipment appropriately.
2. Quickest relief if pain episodes are sudden and severe (pain onset to drug administration - don't have to call/wait for RN to pull medication).
3. PCA pump can be programmed to give bolus doses, continuous infusion, or both.
4. Family or health care professional use of the PCA is not permitted at Partners institutions. However, a clinician bolus dose (from the PCA bag) is separately available as part of the PCA orderset.
5. For patients already on opioid therapy, continuous rate can be estimated based on total daily dose (with appropriate conversions and reduction for incomplete cross tolerance).
6. Patients need to be closely monitored for side effects (constipation, respiratory depression, over-sedation, myoclonus, delirium)
7. Medicine residents can order "General PCA" (for opioid-naïve patients) or "High Risk PCA" (BMI >40, hx OSA, RAAS -2 to -5, age >65). If opioid-tolerant, requiring continuous infusion, or pain difficult to control, consult Palliative Care.

Example Opioid-Naïve* PCA Dosing (will depend on opioid needs of your particular patient)

	Morphine	**Hydromorphone**
Patient Administered (PCA) Dose	1.5 mg	0.2 mg
Lockout Interval (in minutes)	10 minutes	6 minutes
One-Hour Dose Limit (Patient Administered + Infusion)	6 mg	1.4 mg
RN/Clinician Bolus Dose (for breakthrough)	2 mg q30min PRN	0.3 mg q20min PRN
Continuous Infusion Rate**	0 mg/hr	0 mg/hr

*Many cancer patients are NOT opioid naïve and require much higher starting parameters.
**In general, if initiating a continuous infusion, consult palliative care for dosing assistance

Opioid Side Effects:

Constipation (all patients should have a standing bowel regimen!), nausea/vomiting, delirium/confusion, sedation, respiratory depression, pruritis and myoclonus (worse with non-synthetic opioids), hyperalgesia. See next section for details.

Opioid Weaning/Reversal:

Naloxone reverses sedation AND analgesia. Reserve for patients with life-threatening respiratory depression.

- In the hospital, IV naloxone is available. Dilute 0.4 mg (1 mL) of naloxone in 9 mL of saline to yield 0.04 mg/mL. Administer at 0.04 – 0.08mg (1-2 mL increments) q2-3min until response. This diluted approach avoids sudden reversal and precipitation of pain crisis. If no change in respiratory depression after administration, consider other causes.
- In the outpatient setting, naloxone can be administered via intranasal spray. Consider prescribing to patients on opioids.
- Naloxone kits for outpatients: Massachusetts law allows for patients and caregivers to purchase naloxone rescue kits from community pharmacies without a prescription if a standing order is in place. MGH Outpatient Pharmacy has a standing order in place that allows patients to purchase rescue kits. Not covered by insurance.

Managing symptoms in patients with cancer can be challenging, but a wide array of pharmacologic and non-pharmacologic treatment options exist. Below is a summary of treatment methods for the following oncology-related symptoms and signs:

- Nausea/Vomiting
- Shortness of Breath
- Fatigue
- Depression/Anxiety
- Delirium
- Bowel Obstruction
- Insomnia
- Constipation
- Diarrhea
- Loss of Appetite

Nausea/Vomiting (BWH Adult Guidelines for Nausea/Vomiting):

Etiology	Examples	Treatment
Chemical/ Metabolic	Chemotherapy Radiation Electrolyte imbalances Opioid-induced	Ondansetron Dexamethasone* Dopamine antagonists (Olanzapine, Prochlorperazine, Haloperidol, Metoclopramide)**
CNS/Psycho-emotional	High ICP (brain tumor, mets) Anxiety-related	Relaxation techniques Dexamethasone (ICP): 4mg PO/IV BID or 8mg PO/IV daily; Lorazepam (anxiety)
Vestibular	Motion sickness/movement-related	Scopolamine: 1.5mg patch topically q3 days (side effects: dizziness, dry mouth) Meclizine (vertigo): 25 to 100mg daily in divided doses
Abdominal/ Visceral	Reflux, indigestion Constipation Gastroparesis/Ileus GI tract obstruction Panc/biliary obstruction GVHD	PPIs, H2 blockers See constipation section below Metoclopramide** Rad Onc/IR for XRT, stenting, NGT, Venting GJT Stenting, surgical stent/drain, surgery Dopamine antagonists, octreotide
Unknown (empiric treatment)		Prochlorperazine**: 5-10mg PO/IV q6-8h Ondansetron: 4-8mg PO/SL/IV q6h (max 24mg QD) Metoclopramide**: 10-20mg PO/IV q6h Olanzapine**: 2.5-10mg PO/SL qhs Haloperidol**: 1.5-3mg/day, titrate to response Ativan: 0.5-1mg PO/IV Scopolamine: 1.5mg patch topically q3 days Dexamethasone*: 4mg PO/IV BID or 8mg PO/IV Procedural/surgical interventions, as above

*Can affect diagnostic accuracy of biopsies (particularly for heme-based malignancies) and affect treatment regimens (e.g. immunotherapies, CAR-T). If in doubt consult w/ oncology pharmacist and/or attending prior to prescribing.
**Side effects: QTc prolongation, EPS symptoms (akathesia, dystonic reactions, parkinsonism, tardive dyskinesia). Avoid Metoclopramide if suspected bowel obstruction or bowel mets.

Shortness of Breath:

Acute:
Code status: Clarify if code status and goals of care have been discussed/documented.
Work up: Vitals, STAT CXR, EKG, BMP, CBC, LFTs, trop, ABG. Consider CTPE if stable. Page respiratory.
DDx: Pulm edema, effusion, PNA, PE, pneumonitis (radiation, obstruction, drugs), disease progression/lymphangitic spread, COPD, CHF exacerbation, ACS, PTX, anemia, allergic reaction, opioid overdose, muscular weakness, pain
Tx: Oxygen, position, tx underlying cause (e.g. CHF: IV lasix, nitrates; COPD: steroids, nebulizers, BiPAP; PNA: abx).
O2 delivery methods: NC, NRB, Venturi Mask, HFNC, NIPPV, intubation
For acute SOB in a CMO pt: Opioids (hydromorphone/morphine IV boluses, see below), Benzodiazepines (2nd line)

Chronic:
Assess etiology and treat accordingly.
DDx includes (1) underlying lung or cardiac disease (new or existing), (2) cancer progression, (3) disease or treatment complication (i.e. pleural or pericardial effusion, PE, pneumonitis).
Also consider: Pulmonary edema, PTX, PNA, PE, pneumonitis (radiation if ~1-6 months out from XRT, obstruction, drugs), disease progression/lymphangitic spread, COPD, CHF exacerbation, ACS, anemia, allergic reaction, opioid overdose, muscular weakness, pain
Tx: See above and treat underlying cause.

Fatigue (Palliative Care Network of Wisconsin Fast Facts)
Persistent exhaustion and diminished energy related to cancer and/or the treatment of cancer, not relieved by rest, which compromises patient functionality and quality of life.
Causes: Often multifactorial. DDx includes (1) direct side effects from cancer or cancer treatment, (2) sedating medications, (3) psychiatric comorbidities (see below), (4) physiologic compromise (hypoxemia, anemia, organ dysfunction, electrolyte abnormalities, dehydration), (5) nutritional imbalance, (6) sleep disturbance, (7) uncontrolled pain, (8) anemia
Treatment: Treat underlying cause. For empiric tx, non-specific strategies for fatigue can be considered, including methylphenidate 5mg PO or modafinil 100-200mg PO qAM and qNoon (studies mixed, reserve for severe fatigue in pts undergoing chemo or experiencing opioid-related sedation), and dexamethasone 4mg PO BID (if in terminal phase of illness w/ high sx burden)

Non-pharmacologic
(1) Education: Explain cancer-related fatigue to patients and families to normalize the symptoms and set realistic goals around functional status.
(2) Exercise: Meta-analysis suggests that aerobic exercise can improve cancer-related fatigue symptoms. Low to moderate intensity aerobic exercise is ideal (20-30min, several days per week), but benefits may also be seen w/ resistance training (Support Care Cancer 2016;24:969, J Natl Cancer Inst Monogr 2004;32:112).

Pharmacologic
Can discuss w/ oncology and/or palliative care prior to choosing medication for cancer-related fatigue. Generally requires a prior authorization and can still be denied.

Drug Class	Examples	Starting Dose	Dose Range	Side Effects
Stimulants	Methylphenidate: (Ritalin) (Concerta)	2.5 – 5mg QD/BID 18 – 36mg QD	5-20mg BID* Max dose: 72mg QD	N/V, HA, wt loss, insomnia, irritability/ anxiety, caution/avoid w/ a fib
	Dextroamphetamine (Dexedrine)	2.5 – 5mg QD/BID	5-20mg BID*	HA, HTN, CM, wt loss, insomnia, palpitations, irritability/anxiety
	Modafinil (Provigil)	100-200mg QD	200-400mg QD	HA, anxiety, insomnia, decreased appetite, abd pain, nausea
Corticosteroids	Prednisone** Dexamethasone**	7.5 – 10mg PO QD 4mg PO BID	Short course only if potential benefits outweigh side effects	HTN, Cushing's, wt gain, PUD, DM, insomnia, anxiety, skin thinning, immunosuppression
Progestin	Megestrol (Megace)	400mg QD	400-800mg QD	HTN, HA, insomnia, rash, diarrhea, gas, nausea, impotence, weakness, fever

*BID drugs should be given early morning and early afternoon (i.e. 8AM and 2PM) to avoid insomnia.
**Can affect diagnostic accuracy of biopsies (particularly for heme-based malignancies) and affect treatment regimens (e.g. immunotherapies, CAR-T). If in doubt consult w/ oncology pharmacist and/or attending prior to prescribing.

Depression/Anxiety

In a 2014 meta-analysis, the pooled mean prevalence of depression in patients w/ cancer ranged from 8% to 24%, and was highest during treatment (**Psychooncology 2014; 23:121**). Regarding anxiety, a large-scale study in 2012 showed that 34% of outpatients w/ cancer at a tertiary care center endorsed clinically significant anxiety symptoms (**JCO 2012;30:1197**). Thus, important to screen patients for psychological symptoms. No single validated tool for depression and anxiety screening in cancer patients, but PHQ-4 is a quick screen. Always ask patients about mood (feeling down, lack of ability to enjoy things they once did, anxiety) and, if c/f depression, ask about SI.

Depression

- MDD is characterized by SIGECAPS w/ sx for at least 2 wks causing sig distress, not caused by drug use and not explained by bereavement or alternative psych dx.
- Adjustment disorder occurs w/in 3 months of a major stressor and causes distress/functional impairment.

Anxiety

- GAD is characterized by pervasive and excessive anxiety and worry about events or activities, occurring more days than not for at least 6 mos. Associated w/ at least 3 of the following: restlessness, easy fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbance.
- Panic disorder is characterized by recurrent panic attacks, abrupt periods of intense fear or discomfort associated w/ 4 or more of the following symptoms: palpitations, diaphoresis, shaking/trembling, SOB, choking sensation, chest pain, nausea, dizziness/lightheadedness, chills or hot flashes, paresthesia, derealization or depersonalization, and sense of impending doom.
- Acute- or post-traumatic stress disorders occur after emotionally traumatic life event (e.g. cancer diagnoses/treatments, having watched family/friends w/ cancer undergoing treatment or being hospitalized), characterized by anxiety, arousal, numbness, flashbacks, intrusive thoughts, avoidance of triggering stimuli.

Treatment

For MDD and GAD, SSRI + psychotherapy = first line. SNRI's or Mirtazapine 15mg QHS also for simultaneous anxiety/depression. However, these meds need to be monitored over time and should not be started in the hospital w/out clearly stated approval of PCP and/or primary oncologist and plan to treat moving forward. Also, depending on severity of symptoms, consider referral to Psychiatric Oncology and/or Palliative Care in the outpatient setting. For acute anxiolysis, Quetiapine 25mg q6h PRN or Zydis 2.5-5mg q6h PRN, lower doses if elderly. Use BZDs w/ caution due to delirium risk. Avoid long-acting BZD and use lowest dose possible for relief.

Delirium

Acute change in mental status w/ waxing and waning properties that can be classified as hyperactive, hypoactive, or mixed.

Most Common Underlying Causes

1. Medications (benzodiazepines, opioids, steroids, anticholinergic drugs)
2. Electrolyte abnormalities
3. Constipation
4. Urinary retention
5. Sleep deprivation
6. Infection (broad, but UTI most common)

Treatment

Non-pharmacologic: First line treatment for delirium includes reversing the underlying cause and patient re-orientation. Examples of re-orientation include placing the patient near a window to promote normal sleep-wake cycle, providing patients w/ their glasses and/or hearing aids if they usually use these outpatient, reminding the patient about his/her identity and environment as needed, and maximizing exposure to family and friends, in person and by phone. Minimize sleep disturbances - specify in vital signs orders if not checking vitals overnight is acceptable and re-time checks to exclude 10pm to 5am window.

Pharmacologic: Of note, NO pharmacological treatment for delirium is approved by the FDA. BZDs can worsen delirium and should be avoided in most cases. For severe agitation or somnolence due to delirium, consult palliative care. Medications that can help w/ refractory delirium include:

- Melatonin/Ramelteon (melatonin agonist): Pineal gland hormone, use to regulate sleep/wake cycles, starting dose 3mg PO (**Int J Geriatr Psych 2011;26:687**, **JAMA Psych 2014;71:397**). Dose nightly at 6pm for optimal effect, not QHS before bed.
- Quetiapine 12.5-25mg if taking PO or Zydis ODT 2.5-5mg q6h PRN. If IV needed or refractory to these, Haloperidol 0.5 – 1mg IV q4h PRN (**Cochrane Database 2020;1:CD004770**)

- For hyperactive delirium in patients w/ terminal delirium, consider Haloperidol 0.5-1mg IV q4h PRN and lorazepam 0.5-1mg IV q4h PRN. Can liberalize doses and intervals if CMO.

Bowel Obstruction

A common complication for GI cancers and cancers metastatic to the abdomen.

Management options:

- Esophageal obstruction: (1) External beam RT (consult Rad Onc), (2) Endoscopic laser therapy (consult GI), (3) Endoscopic/fluoroscopic stenting (consult GI or IR)
- Gastric or duodenal obstruction: (1) NGT decompression, (2) Venting G-tube (placed by IR or surgery) w/ consideration of GJ or J-tube for nutrition depending on GOC, (3) Endoscopically/fluoroscopically placed stent across site of obstruction (consult GI), (4) Janeway gastrostomy (surgical gastro-cutaneous fistula), (5) Laparoscopic/open gastrojejunostomy
- Pancreaticobiliary obstruction: (1) Stent/drain placement across obstruction (consult GI for ERCP or IR for transhepatic approach), (2) Laparoscopic/open cholecystojejunostomy
- Adjuvant medications: PPI to reduce gastric secretions, Carafate for patients w/ ulcerated esophageal or gastric lesions, Octreotide for secretions and high-volume output conditions, scopolamine to decrease peristalsis and intestinal secretions, and dexamethasone to decrease inflammation. Metoclopramide, w/ its promotility and antiemetic properties could be utilized in a partial obstruction, however should be avoided in a complete bowel obstruction.

See Section 9.2 of this manual for more information on Bowel Obstruction management

Insomnia

Dissatisfaction w/ sleep quantity/quality, associated w/ difficulty initiating or maintaining sleep, early AM waking w/ inability to return to sleep, sleep disturbances causing impaired daytime functioning >3 nights/week x > 3 months despite adequate opportunity to sleep (**Ann Intern Med. 2016;165:125**).

Underlying causes:

- Acute insomnia: (1) Situational stress (occupational, interpersonal, financial, academic, medical); (2) Environmental (noise); (3) Adjustment disorder (death or illness of a loved one)
- Chronic insomnia: (1) Medical disorders: Cancer/cancer pain, arthropathies, CHF, COPD, ESRD, GERD, HIV/AIDS, hyperthyroidism, BPH, stroke (2) Medications: SSRIs/SNRIs, anti-epileptics (lamotrigine, phenytoin), anti-neoplastics, beta-blockers, bronchodilators (beta-agonists), CNS stimulants (methylphenidate, dextroamphetamine, nicotine), steroids, oral contraceptives, thyroid hormone; (3) Primary sleep disorder: Restless leg syndrome, OSA, periodic limb movement disorder; (4) Psychiatric disorders: anxiety disorders, bipolar disorder, schizophrenia, MDD, PTSD; (5) Sleep-wake schedule disorder: Irregular sleep-wake cycle, jet lag, shift work; (6) Substance use: Alcohol, smoking, caffeine, stimulants.

Treatment

Non-pharmacologic: (1) Sleep hygiene (e.g. limit daytime naps, avoid bright light/screens/phones near bedtime, limit caffeine and stimulants to mornings, quiet/dark/cool sleeping environment); (2)Cognitive behavioral therapy (CBT-Insomnia); (3) Exercise

Pharmacologic (Out-of-Hospital): When selecting among various sedative-hypnotic medications, choose on the basis of the type of insomnia (sleep onset or sleep maintenance) and the duration of effect.

Drug	Initial Dose	Common Side Effects	Avoid in:
For Treatment of Sleep Initiation			
Ramelteon (Rozerem) [Melatonin agonist]	8mg QHS (30m before bed)	Dizziness, fatigue, HA, unpleasant taste, N/V, sleep-driving, worsens mood & SI in pts w/ depression	Liver disease; Interacts w/ Cipro/Rifampin
Trazodone	25-50mg QHS (25mg in elderly)	Causes QTc prolongation, hypotension, serotonin syndrome	MAOi use, suicidal thinking/severe depression, Linezolid therapy
Triazolam (Halcion)* [short-acting BZD]	0.25mg QHS, 0.125 low wt, elderly, max 0.5mg	Daytime drowsiness, dizziness, increased fall risk/hip fractures in elderly	Elderly, pregnancy, OSA, AUD

Zaleplon (Sonata)* [non-BZD hypnotic]	10mg QHS (5mg low wt), max 20mg	Headache, pain, dizziness, GI issues, arrhythmia, hallucinations	Elderly, liver disease, pregnancy, OSA, AUD
Zolpidem (Ambien)* [non-BZD hypnotic]	5mg (F), 5-10mg (M) QHS	Anxiety, depression, mood alterations, hallucinations, memory/driving impairment, increased fall risk	Elderly, liver disease (HE), pregnancy, OSA, AUD
For Treatment of Sleep Maintenance			
Doxepin (Silenor, Sinequan)* [sedative TCA]	3-6mg QHS (30m before bed)	Sedation, fatigue, weakness, lethargy, dry mouth, constipation, blurred vision, HA	Untreated narrow angle glaucoma, risk of urinary retention, interacts w/ MAOI
Suvorexant (Belsomra) [orexin receptor antagonist]	10mg QHS, can up titrate 5mg q2 weeks, max 20mg	Amnesia, anxiety, hallucinations, sleep-driving, worsens mood & SI in pts w/ depression, sleep paralysis, hypnagogic/ hypnopompic hallucinations	Severe liver disease
For Treatment of Both Sleep Initiation and Maintenance			
Eszopliclone (Lunesta)* [non-BZD hypnotic]	1mg QHS, max 3mg	Unpleasant taste, myalgias, memory impairment, depression, anxiety, increased risk of accidental injury	Elderly, liver disease (HE), pregnancy, OSA, AUD
Temazepam (Restoril)* [Intermediate-acting benzo]	15-30mg QHS, 7.5mg in elderly/frail patients	Daytime drowsiness, dizziness, depression, increased cancer incidence	Elderly, liver disease (HE), pregnancy, OSA, AUD
Zolpidem XR (Ambien CR)* [non-BZD hypnotic]	6.25mg (F), 6.25 – 12.5mg (M) QHS	See Zolpidem above.	Elderly, liver disease (HE), pregnancy, OSA, AUD

*Avoid in patients w/ delirium risk (e.g. elderly, dementia, infection, dehydration, immobility, malnutrition)

Pharmacologic (In Hospital): Distinct from insomnia, we have a distinct set of medications that we use to help patients cope w/ trouble sleeping during hospitalization.

Medication	Starting Doses	Take Note
Melatonin	3-8mg QHS (several hours prior to sleep)	Avoid in Hypotension, hx seizures
Trazodone	50mg QHS starting dose (25mg in elderly)	Causes QTc prolongation, hypotension, serotonin syndrome
Quetiapine	12.5 – 50mg QHS starting dose	Causes QTc prolongation, orthostatic hypotension, EPS
Mirtazapine	7.5-15mg QHS (lower dose more effective for sleep)	Lower doses better for insomnia, higher doses for depression/appetite
Lorazepam*	0.5-1mg QHS	Can worsen delirium/confusion, can lead to dependence

*Avoid in patients w/ delirium risk (e.g. elderly, dementia, infection, dehydration, immobility, malnutrition)

Constipation

- Risk of constipation higher in hospital due to inactivity, ↓ PO intake, and med effects, particularly opioids/anticholinergics.
- Write all patients for at least PRN senna and polyethylene glycol on admission unless contraindicated (i.e. diarrhea, possible mechanical obstruction), then escalate PRN (see below).
- Unless contraindicated, ↑ bowel regimen when starting/increasing opioids.
  - Senna 2-4 tablets PO QD – BID standing and Miralax 17g PO QD PRN or standing
  - If insufficient, add Dulcolax suppository 10 mg daily (avoid in neutropenic and plt < 50k patients)
  - If NPO, can consider Reglan 10mg IV q6h or suppository

- SubQ methylnaltrexone is only for opioid-induced constipation. May be added for patients who have failed multiple bowel regimen therapies and have no signs of bowel obstruction.
- If refractory, ensure no fecal impaction in rectal vault w/ an abdominal x-ray (requires manual disimpaction), then consider enemas, magnesium sulfate, lactulose, or colonoscopy prep (Nulytely)

Diarrhea:

- Important to identify cause of diarrhea, such as infection, and address etiology prior to symptomatic treatment. Also must be aware that antimotility agents can mask the amount of daily fluid lost, since fluid may pool in the intestine.
- Loperamide (Imodium): 4mg initially, then 2mg q4h or after each loose stool until controlled (max dose 16mg/day).
- Diphenoxylate (Lomotil): 5mg up to 4x/d until controlled (maximum dose 20mg/d), then reduce dose as able. Maintenance dose may be as low as 25% of initial daily dose. Caution due to anti-cholinergic side effects especially in the elderly.

Loss of Appetite/Cancer Cachexia:

- Corticosteroids
  - Dexamethasone: max 4mg/day PO, use only if treatment days to weeks anticipated, duration of appetite stimulation often short-lived. Risk of myopathy, cushingoid body habitus, peptic ulcers, mood lability, insomnia.
  - Can also use prednisolone (25mg) or methylprednisolone (20mg)
- Progesterone analogs
  - Megestrol acetate: max 800 mg/day PO, use if greater than weeks of life expectancy and therapy. However, does have an increased risk of edema and potentially life-threatening thromboembolic events. Thus, aim for lowest effective dose. Do not use w/ concomitant chemotherapy (thrombogenic). Can also increase suppression of HPA axis (caution in presence of serious infection, surgery, or trauma) and, in men, cause symptomatic androgen deficiency.
- Cannabinoids (THC)
  - Dronabinol, Nabilone, CBD oil, inhaled marijuana: no evidence to increase appetite in cancer anorexia/cachexia.
- Serotonin antagonists
  - Cyproheptadine: use in patients w/ carcinoid syndrome, 8mg PO TID
  - Mirtazapine: weak data, but ↓ risk vs progesterone and dex and may ↑ weight gain and appetite, 15mg PO QHS

Additional Symptom Management (Palliative Care Network of Wisconsin Fast Facts)

Symptom	Management
Mucositis	Grades: (1) Injection, erythema, mild pain; (2) Patchy, serosanguinous discharge, moderate pain; (3) Confluent fibrinous mucositis, severe pain; (4) Ulceration, hemorrhage, necrosis; (5) Death from mucositis Treatment: Local anesthetics for pain management (Magic Mouthwash: salt water rinses, Maalox, Benadryl, Lidocaine, Nystatin; Gelclair). Liquid, oral, parenteral, or IV opioids may be required for pain management. Oral ketamine can also be considered. Low threshold to consider superinfection and obtain cultures.
Oral Candidiasis	Nystatin suspension 200,000 – 500,000 units, 4-5x/d, 7-14d, Clotrimazole (10mg troche) 5x/day For immunocompromised pts: systemic therapy (Fluconazole 200mg x1, 100mg x14 days)
Xerostomia (dry mouth)	Stop/decrease meds that may be causing sx as able (anticholinergics, antihistamines, antipsychotics, sympatholytics, opioids) Stim residual gland fxn: sugarless gum, candies & cholinergic agonists (i.e. pilocarpine, 5mg TID) Saliva substitutes: Biotene (gel or gum), artificial saliva Ice chips, oral hygiene, oral hydration
Secretions	Pooled secretions lead to a "death rattle" at end of life. Disturbing to observers, although less bothersome to patient. Prepare family, position pt to facilitate postural drainage, stop feeding/fluids, don't deep suction (uncomfortable to pt) Glycopyrrolate 0.2-0.4mg IV q4h PRN. Alternatives: scopolamine patch, atropine (SL, IV), hyoscyamine (PO, SL)
Hypercalcemia of malignancy (HoM)	1. Order PTHrP to confirm. 2. Tx dehydration w/ NS 200-500ml/hr to filter calcium for goal UOP 100 mL/hr 3. Consider loop diuretics (Lasix) blocks calcium reabsorption but should only be used after correcting dehydration.

	4. Discontinue meds that can increase serum calcium (lithium, calcitriol, thiazides). 5. Bisphosphonate - zoledronic acid (4mg), pamidronate (60-90mg). Full efficacy 2-4 days, response lasts 1-3 weeks. May repeat in 7 days, if inadequate response then q2-3w PRN. Use w/ caution in renal failure, especially if multiple myeloma driving hypercalcemia. Doses of zoledronic acid and pamidronate studied in for HoM in patients w/ SCr up to 4.5 mg/dL w/out dose adjustment. 6. Dialysis can be used for acute/chronic renal failure.
Malignant pleural effusion	Chemo/RT if available and w/in GOC, repeated thora/paracentesis, indwelling Pleur-X catheters.
Malignant ascites	Consult IR to discuss options. Paracentesis: Can provide immediate relief for large volume uncomplicated ascites → think about sending for cytology and micro. Drainage catheters: For patients who require frequent drainage. Risks of infection, leakage, occlusion. Pigtail catheter: simple, all-purpose, but prone to complications when used over extended duration. Tunneled Catheter: promotes scarring around an antibiotic cuff. Lower risk of infection, leakage. Used for patients w/ life expectancy >1mo. Vascular shunts: Peritovenous shunt: Channels peritoneal fluid in benign ascites back into circulation via IVC. No known increased risk of spreading tumor cells in malignant ascites. Usually for patients w/ life expectancy 1-4 months. Occlusion rate 24%. TIPS: Shunt between portal and hepatic vein, though only effective for patients w/ portal HTN. Hyperthermic Intraperitoneal Chemotherapy: By surgical oncologists. Recovery 3-6 months.
Neoplastic meningitis	Dx: LP. Often portends a poor prognosis. Tx: XRT, high dose/intrathecal chemotherapy, pharmacological pain management

Overview of End of Life Care

Code Status Discussions:

General Considerations

- Ideally, code status should be confirmed and reflected in Epic at the time of admission. Given sometimes unclear prognosis of underlying cancer, often good to include floor attending +/- outpatient oncologist in these discussions - do not presume full code
- Confirm directly w/ the patient/HCP/surrogate, MOLST, and/or prior documentation by outpatient providers
- Consider revisiting discussion if a patient's clinical status changes, or if code status is deemed inappropriate for the clinical setting
- While code status reflects a subset of a patient's preferences, it does not reflect all of a patient's goals and values.

Survival Outcomes (**Palliative Care Network of Wisconsin**, **JAMA 2005;293:2265**)

- Out-of-hospital cardiac arrest: pre-hospital survival 26-29%; survival to hospital discharge 10-12% (varies by disease); survival w/ good neurologic function ~9%
- In-hospital cardiac arrest: immediate survival 54%, survival to discharge 20-25% (varies by disease)
  - Favorable outcomes: ACS, drug overdose, drug reaction (up to 40% survival)
  - Unfavorable outcomes: age >80 (<10% survival), multiorgan failure, sepsis, metastatic CA, renal dz, dementia
- Rates of clinically significant neurologic disability improving, but remain ~28-30% in those who survive in-hospital arrest
- Post-arrest complications include hypoxic-ischemic brain injury, rib fractures, pulmonary contusion, prolonged ICU care

Tips (**JAMA 2003;289:2387** & **2000;284:2476**)

- Initial tips:
  - Be prepared: Plan the conversation ahead of time. Know details of your patient's condition and prognosis.
  - Do not offer DNI alone (i.e. Full Code / DNI), as resuscitation almost always requires intubation
- Information-gathering code status discussion (patients you would expect to be full-code) – suggested scripted conversation:
  - Setup/invitation: "Would it be okay if we did some emergency planning? I want to talk about a procedure called CPR."
  - Pt's understanding: "What do you know about CPR? Do you have any personal experience w/ CPR? Have you spoken w/ other doctors about CPR?" [If appropriate, explain CPR in non-medical terms – see below].
  - Knowledge of current code status: "Right now, if your heart were to stop, you would receive CPR. Is this consistent w/ your goals?"
  - Normalize re-assessment/forecast the future: "At some point, your doctor may no longer recommend CPR because it would be unlikely to help. At that time, your team will talk w/ you more."
- Decision-making code status discussion (recommendation of DNR/DNI) – suggested outline:
  - Setup/seek permission: "I would like to talk about the future w/ your health. Would that be okay?"
  - Pt's understanding/prognostic awareness: "What is your understanding of your illness? Looking to the future, what are your hopes? What are your worries? Would it be ok if we spoke more about what lies ahead?"
  - Share worry: "I am hoping for you to have that time at home w/ your family and I am worried that something serious could happen in the next few weeks to months. I wish that we didn't have to worry about this. If your health were to worsen, what is most important? Given where we are w/ your illness, I recommend we do some emergency planning and discuss CPR. CPR is a medical procedure that we would do if you were to die, that is if your heart were to stop and you were to stop breathing. CPR includes pressing on your chest to pump the heart and the use of a breathing machine to help you breath."
  - Make recommendation: "I am worried that CPR is no longer a helpful treatment. I worry that it will not help you live longer or better, and that it could cause you suffering in the dying process. If something serious were to happen, I recommend allowing a natural death and not performing CPR. Is this okay w/ you?"
  - Record this conversation in EPIC. In the Advanced Care Planning Guide, click on Serious Illness Conversation and complete the components. To pull this into your note use the dot-phrase ".acpsilast".

Hospice

Hospice is the model for quality comfort-oriented care for patients and their families facing a life-threatening illness. Hospice provides a comprehensive multidisciplinary team approach to the management of total pain: physical, spiritual, psychological, social. To receive hospice care, a patient must have a physician certified prognosis of <6 mos. Patients typically forgo further curative or life-prolonging treatmnents of the terminal condition. Although a code status of DNR/DNI may be appropriate, it is not required for a patient to be hospice eligibile per Medicare guidelines.

Hospice provides access to an interdisciplinary team inclusive of a physician, nurse, social worker, counselor (spiritual, bereavement and/or dietary). Hospice can also provide the services of PT/OT/SLP, homemaker, home health aide, and volunteer. Hospice care typically provides durable medical equipment such as hospital beds, commodes, wheelchairs, oxygen and respiratory equipment, surgical dressings, colostomy bags to name a few. They will cover the cost of prescriptions needed to control the symptoms of the terminal illness.

Hospice Levels of Care:

Routine Home Care:

The majority of hospice care is provided w/in the home, which includes private residences, nursing homes, and residential facilities. This is an ideal setting for patients whose pain and non-pain symptoms are well-controlled. Patients will have access to the interdisciplinary team including a hospice nurse who at minimum will visit 1 hour per week or more frequently as determined by patient's needs. The majority of the care will be provided by the family, friends, or hired caregivers. In general, hospice at home precludes the use of IV medications (although oral, sublingual, and suppositories can still be used).

Continuous or Crisis Home Care:

This is provided when a patient has an acute worsening of pain or other symptoms, requires continuous care to manage the symptoms, and wishes to remain at home. In these situations, nursing services, possibly supplemented w/ a home health aide and/or homemaker services, are provided on a continuous basis, ranging from 8 to 24 hours a day for brief periods of crisis.

Skilled Nursing Facility with Hospice:

Although home is generally preferred, particularly for the sake of easier visitation by family (especially w/ the COVID-19 pandemic), patients who are unable to be discharged home due to medical complexity or deconditioning and are not imminently dying (would push you toward GIP), may be able to receive end-of-life care at a SNF w/ an associated hospice. Ask case management for help locating such facilities. A "hospice house" similarly is a facility that is a higher level of care than home hospice, but not quite at the level of inpatient hospice, where patients can continue comfort-oriented care.

General Inpatient hospice (GIP):

GIP level of care may be provided in a hospice unit, and in acute care hospitals or skilled nursing facilities w/ contracted hospice beds. Patients must have uncontrolled pain or other symptoms and distress that are not able to be effectively or safely managed in another level of care or setting. A patient who qualifies for GIP level of care could be considered for admission to MGH GIP Hospice if their prognosis is less than 2 weeks. If admitted to GIP, patient will stay at MGH and transfer (service, not physically in most cases) to a palliative care team.

For patients not ready to transition to Hospice care, they can be connected w/ a a visiting nurse agency w/ a hospice branch, so that at a later date, the patient can be "bridged to hospice"

Hospice discussions w/ seriously ill patients should always take place in the context of the larger goals of care. If you think one of your patients may be ready for transition to hospice, it is important to start a discussion w/ case management and consider consulting palliative care after confirming w/ oncologist that it is an appropriate time.

Adapted from the Palliative Care Network of Wisconsin and Code of Federal Regulations, Title 42. Hospice Care. 2017.

Performance Status

The single most important predictive factor in the mortality of cancer patients is Performance Status ('functional ability,' 'functional status'): a measure of how much a patient can do for themselves, their activity and energy level. Most commonly used measures of functional status are ECOG (0=normal, 5 = dead) & Karnofsky (100 = normal, 0 = dead). Median of 3 months survival correlates w/ Karnofsky score of ≤ 40 or ECOG ≥ 3.

Death and Dying

Stages of Death

- Discuss prognosis in terms of ranges (minutes-hours, days-weeks, weeks-months) rather than specific dates; clinical trend is the most valuable prognostic tool.
- Early: Bedbound, loss of interest in food/drink, cognitive changes, drowsiness, decreased speech
- Middle: Lethargy and stupor, fever
- Late: Coma, cool extremities, terminal respiratory secretions as the upper airway relaxes ("death rattle"), loss of radial pulse, altered respiratory pattern (Cheyne-Stokes) w/ increased jaw movement, fevers
  JAMA. 2005; 293 (18): 2265 – 71. JAMA. 2003; 289(18):2387 & JAMA. 2000; 284(19):2476

Prior to Death:

- Involve family +/- chaplaincy (avail 24/7) +/- other care team members (i.e. PCP). Ask family about religious/cultural prefs.
- Consider early contact w/ New England Organ Bank (NEOB) @ 800-446-6362. NEOB determines eligibility for donation. They are trained to discuss donation w/ families. You SHOULD NOT discuss donation w/ the family.
- When passing off a patient who may die, prepare the paperwork (see below).

Pronouncement and Reporting a Patient Death

PROUNCEMENT: Introduce yourself to the family, explain what you are doing, express condolences, ask for preferences for staying or leaving room for exam.
FEEL for a pulse, LISTEN for heart sounds/breath sounds (>60 s), and NOTE time at the end of your exam, which will become the time of death.
QUESTIONS for next of kin (NOT HCP, next of kin (NOK): Spouse>Children>Other Family)
Confirm and document FULL NAME and PHONE NUMBER
Does the next of kin request an AUTOPSY? (can offer dx, identify heritable conditions, contribute to science/ed)
Ask the family if they would like to see a chaplain
If no NOK in room, call to notify NOK of patient's death, clarify if anyone will be coming to visit the body prior to morgue
Patient's body will be kept at MGH until the funeral home calls MGH (path 617-726-2967) and arranges for pick up
ONCE YOU LEAVE THE ROOM:
Step 1: Notify ATTENDING and PCP. E-mail if death was expected, page attending if unexpected.
Step 2: Obtain "Report of Death" form from OA. Fill out in black ink. If any mistakes, you will need to start over.
Step 3: Log into EPIC and CALL New England Organ Bank: 800-446-6362. Will need patient demographics, cause of death. May require: hx of cancer, recent infections, hx dementia, other PMHx.
Step 4: Call the Admitting Office (6-3393) to inform them of the death. They will ask re: diagnosis, Medical Examiner involvement (you do not necessarily have to call, see indications on form), and NEOB information.
Step 5: The "Report of Death" goes to admitting w/ the patient chart. Chart cannot leave the floor until the form is completed. Patient is transported to the morgue by nursing.
Step 6: Document a brief "Significant Event: note. Smart-phrase: ".deathnote".
Step 7: Complete brief discharge summary using "Deceased Patient" portion of the Discharge tab in EPIC.
Adapted from the MGH White Book

Feedback

We warmly welcome any specific suggestions for how to improve this manual. Please contact the editors at any time w/ comments, suggestions, and errata.

Thank you in advance for your constructive comments and commitment to improving this manual!